EL816576472US PATENT

Docket No.: HMR2041 US NP1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Kurt M. Kesseler

Serial No.: 09/760,590

Filed: 01/16/01

Title: Ethanol Solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one

Examiner: Celia C. Chang

Art Unit: 1625

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APPEAL BRIEF UNDER 37 C.F.R. 1.192

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Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

This is an appeal from the Final Rejection of Claims 10 to 19. A copy of these claims is attached hereto as Appendix I.

RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to appellant, appellants' legal representative or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant pending appeal.

STATUS OF THE CLAIMS

Original claims 1-9 were cancelled and new claims 10-19 were added. Claims 10-19 remain in the application and claims 10-19 have been finally rejected.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection.

SUMMARY OF INVENTION

The invention relates to an ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride (termed as Form II) characterized by X-ray powder diffraction data (claims 10-12; specification page 1, line 32, to page3, including table 1), processes for making Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate (claims 13-15; specification page 4, lines 4-20; page 5, line 20 to page 8, line 20), a pharmaceutical composition comprising a therapeutically effective amount of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate and a pharmaceutically acceptable carrier (claim 16; specification page 5, lines 1-11), and to methods of using Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate for treatment of cancer (claims 17-19; specification page 8, lines 22-27).

ISSUES

At issue with respect to the final office action (Paper No. 10) is whether claims 10-19 are obvious over Kim U.S. 5,908,934, in view of Cheronis ["Semimicro Experimental Organic Chemistry", DeGratt, p. 32-35 (1958)] and Evans ["An Introduction to Crystal Chemistry", Cambridge Press, p. 393-397 (1964)].

An Advisory Action (Paper No. 15) mailed on June 19, 2003, indicates that the proposed amendments filed May 2, 2003, will not be entered on the basis that new issues requiring further consideration and/or search are raised, that the Shutske declaration and request for reconsideration was considered but does not place the application in condition for allowance, and that the filing of a Notice of Appeal on May 2, 2003, was acknowledged. The Advisory Action and the comments attached to the Advisory Action will be separately discussed at the end of this Appeal Brief.

GROUPING OF CLAIMS

The patentability of claims 10-19 will depend on the reversal of the rejection under 35 U.S.C. 103(a), and accordingly claims, 10-19 stand or fall together.

ARGUMENT

The invention claimed in all of Appellants' finally rejected claims 10-19 relates specifically to Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate (the compound per se is also know as flavopiridol). Claims 10-12 pertain to composition of matter; claims 13-15 pertain to processes for making; claim 16 pertains to a pharmaceutical composition; and claims 17-19 pertain to a method of treating cancer with said Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate.

The final rejection (Paper No. 10) is based on the Office's allegation that Kim '934 (Example 2D, column 9, lines 19-67) explicitly recites *that "...the residue was stirred in MeOH (20 ml) at reflux....and ethyl ether (50 ml) was added....precipitated solid was....washed with ethyl ether three times and dried to afford a solid, 6.7 g which contained the title compound methanol".* The Office alleges that *"this explicit description provided evidence that a method was made under reflux and precipitated, washed to obtain such 'compound methanol' which is consistent with the nomenclature of solvates/hydrates i.e. magnesium sulfate 7 H_2O or magnesium sulfate hydrate.* State of the art reference Evans ["An Introduction to Crystal Chemistry", Cambridge Press, p. 393-397 (1964)] was cited as describing *"that a clathrate is a crystalline organic material with small solvent being uncaged, is the mechanical embracing of organic material and solvents. Therefore, the explicit naming of the 'compound methanol' product by Kim '934 (column 9, line 53) is evidence that a solvate/clathrate instead of compound per se was indicated by Kim."* Also, the Office alleges *"that since Kim '934 is a U.S. patent and that an explicit description and facts have been pointed out to applicants as to the nature of the product, applicants allegation [the] that product of Kim '934 is not convincing to applicants as being a solvate must be supported by a preponderance of evidence since such allegation of inoperability of a U.S. patent must be factual (Trans-World vs Al Nyman 219 USPQ 1059)."*

Appellants respectfully traverse the Office's rejection of claims 10-19 under 35 U.S.C. 103(a) over Kim '934 in view of Cheronis and Evans, based on the well established legal principles, that:

A. Obviousness under 35 USC 103 is a legal conclusion based on factual evidence, that motivation must come from the prior art and not applicant's specification (hindsight reconstruction) and that the application of Kim '934 as a reference is inappropriate.

B. There must be suggestion or motivation in the prior art to support combining the cited references. Kim '934 teaches away from Appellants' claimed invention.

It is respectfully submitted that the following arguments convincingly support Appellant's assertions.

A. Obviousness under 35 USC 103 is a legal conclusion based on factual evidence and that the application of Kim '934 as a reference is inappropriate.

Appellants respectfully traverse the Office's position concerning the statement that the "*explicit*" description by Kim '934 provided "*evidence that a method* **[??]** *was made under reflux and precipitated, washed to obtain such 'compound methanol' which is consistent with the nomenclature of solvates/hydrates.*" The critical sentence in Kim '934, column 9, lines 53-56, reads:

"The precipitated solid was filtered, washed with ethyl ether three times and dried to afford a solid, 6.7 g which contained the title compound methanol."

The phrase "title compound" in the above-quoted sentence refers to the known compound (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one, that is also known as flavopiridol. As discussed herein, Appellants maintain that the phrase "title compound methanol" in the above-quoted sentence is ambiguous and not readily understood by one of ordinary skill in the art with respect to the meaning or context of the word "methanol" in the absence of supporting physical and/or spectral data or other explanatory statements. Arguendo, even if it were to be considered that the above-quoted sentence is purportedly indicative of making a methanol solvate (as the Office contends), the

description by Kim '934 fails to provide any convincing evidence such that one of ordinary skill in the art would believe that Kim '934 indeed made the methanol solvate following the procedures described therein. In support of this, Appellants provided the following documents and analysis.

1. The declaration of Gregory M. Shutske (Appendix II), one skilled in the art of organic chemistry and whose native language is English, was included with the response filed on May 2, 2003, to the final rejection (Paper No. 10). Shutske's declaration maintains that one of ordinary skill in the art would not be able to determine with any degree of certainty from the phrase "title compound methanol" whether or not the form of the title compound obtained by Kim '934 was a solvate/clathrate in the absence of additional spectral or analytical data for two reasons.

a. First, the word "hydrochloride" is omitted from the phrase "title compound methanol" and that omission, in itself, brings into question the reliability of the phrase "title compound methanol" to accurately describe the form of the title compound so obtained.

b. Second, the phrase "title compound methanol" is not written in an explicit form that is consistent with the nomenclature of solvates/hydrates as would be clearly understood by one of ordinary skill in the art. Examples of properly written art-recognized descriptions of compounds explicitly named to indicate solvation are provided in paragraph 7 of the Shutske declaration.

2. Appellants also filed with their May 2, 2003, response a copy of page 298I from "Naming and Indexing of Chemical Substances for Chemical Abstracts", a reprint from Appendix IV from the Chemical Abstracts 1997 Index Guide, and drew attention to the second paragraph in section 192 to further support how solvates are explicitly named or classified by Chemical Abstracts Service. (Appendix III)

In view of the foregoing Shutske declaration and Chemical Abstracts 1997 Index Guide page 298I, Appellants maintain that the Office's reliance on the Kim '934 prior art reference to support the obviousness rejection is improper for the following reasons.

1. Obviousness under 35 USC 103 is a legal conclusion based on factual evidence (Stratoflex, Inc. v Aeroquip Corp., 713 F.2d 1530, F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983)

MPEP§ 2142 states that "In view of all factual information *(emphasis added),* the examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person" [a hypothetical person of ordinary skill in the art].

The Office's analysis is clearly not based on factual evidence since the identity of the form of the 6.7 g solid obtained by Kim '934 in the above-quoted sentence is not ascertainable with any degree of certainty by one of ordinary skill due to the ambiguous wording of the phrase 'title compound methanol", and the fact that no supporting physical or spectral data or explanatory statements were provided to characterize the 6.7 g solid so obtained. This conclusion is supported by the Shutske declaration. Furthermore, due to the absence of detail in the above-quoted sentence from Kim '934 concerning how the 6.7 g solid was dried, it is impossible to faithfully reproduce the form of the Kim '934 6.7 g solid to confirm or refute the Office's position that Kim '934 was, even inadvertently, in possession of the methanol solvate form of the title compound. The Office indicates that Appellants' should provide factual evidence that the "product" cannot be a clathrate, but the absence of detail in the above-quoted sentence in Kim '934 renders it impossible to knowingly reproduce the form of the 6.7 g solid so obtained by Kim '934. At the same time the Office is rejecting Applellant's claims in the complete absence of factual information concerning the true form of the "title compound methanol" as the basis for its determination that the claimed invention as a whole would have been obvious at that time to a person of ordinary skill in the art.

2. Motivation must come from the prior art and not applicant's specification [In re Dow Chem. Co. v American Cyanamid Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531-31 (Fed. Cir. 1988)]

The obviousness rejection is based on the Office's presumption, in the absence of any supporting evidence, that the ambiguous phrase "title compound methanol" establishes that a methanol solvate was obtained by Kim '934. Appellants' application

clearly recites that the title compound (flavopiridol) crystallizes into numerous solvates including the methanol solvate (Specification page 1, Appendix IV). Thus, the Office's presumption that the phrase "title compound methanol" is an "*explicit naming and is evidence that a solvate/clathrate instead of compound per se*" was obtained by Kim '934 appears to be unsupported by anything except impermissible hindsight reconstruction based solely on Appellants' disclosure, that the form of the 6.7 g solid actually obtained by Kim '934 is a methanol solvate. Appellants submit that Office's presumption of evidence that a solvate/clathrate was obtained is not supported by factual evidence or unambiguous description in the Kim '934 disclosure.

3. Prior art references must teach or suggest all the limitations of the claims (In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496).

The ambiguous nature of the phrase "title compound methanol" in the disclosure of Kim '934 is not remedied by the disclosures of the secondary references.

Indeed, the Evans "state of the art" reference is merely a textbook discussion of how phenol and quinol form crystalline compounds with argon, oxygen, sulfur dioxide, hydrogen chloride, methanol and many other small molecules. It should be appreciated that the Evans reference specifically mentions the fruitful use of X-Ray studies to study such "host-guest" compounds in the solid state, and thus the Evans reference acknowledges the importance of factual evidence for the study of "host-guest" compounds. However, Evans is little more than a generic reference that indicates that organic compounds may form complexes with solvent and/or other "guest" molecules, a fact well known in the art of organic chemistry. The Cheronis "Semimicro Experimental Organic Chemistry" reference (pages 32-35) is also a text book reference concerning generic selection of recrystallization solvents and recrystallization techniques that are also well known in the art of organic chemistry.

The seminal issue is that the combination of the ambiguous phrase "title compound methanol" in the absence of physical and/or spectral data or explanatory statements renders it impossible for Kim '934 to teach or suggest all the limitations of Appellant's claims either alone or in combination with the two cited secondary Evans and Cheronis references. Thus, there is no teaching or suggestion to make Appellant's claimed invention nor is there

any reasonable expectation of success to be found in the prior art teachings. Accordingly, the Office's analysis required by MPEP§ 706.02(j) to establish a prima facie case of obviousness is flawed since Kim '934 alone or in combination with the secondary references fails to clearly and factually disclose all the elements of the claims. Thus, the Office's application of Kim '934 as a reference is improper. Appellants having rebutted the Office's assertion of a prima facie case, it is now the Office's burden to provide factual evidence to support its position.

B. There must be suggestion or motivation in the prior art to support combining the cited references.

Kim '934 teaches away from Appellant's claimed invention.

In the final rejection (Paper No. 10), the Office alleges *"that the rejection of Claims 1-9 under 35 USC 103(a) as being unpatentable over Kim U.S. 5,908,934 ('934) in view of Cheronis ["Semimicro Experimental Organic Chemistry", DeGratt, p 32-35 (1958)] and Evans ["An Introduction to Crystal Chemistry", Cambridge Press, p 393-397 (1964)] is applicable to newly added claims 10-19 for reason of record. The Office alleged that the gist of applicant's argument is that the description of Kim '934 at col. 9, lines 53, is not convincing to applicants that this is a solvate. This is not persuasive. Please note that Kim et al [gave] explicit*[ly] *described that "...the residue was stirred in MeOH (20 ml) at reflux...and ethyl ether (50 ml) was added...precipitated solid was...washed with ethyl ether three times and dried to afford a solid, 6.7 g which contained the title compound methanol." Please note that this explicit description provided evidence that a method was made under reflux and precipitated, washed to obtain such "compound methanol" which is consistent with the nomenclature of solvates/hydrates i.e. magnesium sulfate $7H_2O$ or magnesium sulfate hydrate. As it has been provided by the state of the art reference Evans, that a clathrate which is crystalline organic material with a small solvent being uncaged, is the mechanical embracing of organic material and solvents. Therefore, the explicit naming of the compound product by Kim '934 is evidence that solvate/clathrate instead of compound per se was indicated by Kim."*

In the previous office action (Paper No. 7), the Office alleged *"that Kim '934 disclosed all the elements of the claims except the solvent employed by Kim '934 is*

methanol and during the crystallization stage a paired solvent of methanol/ether was used, while instant claims are drawn to the homologous ethanol. Cheronis teaches that the choice of solvent in crystallization is empirical and one should experimentally select under the general guidelines (see p 32, section 5.3), and that when the solubility of the compound in a particular solvent is too high, solvent pair may be employed (see p 35)." The Office further alleged *"that one having ordinary skill in the art would find the claimed product and process prima facie obvious over Kim because:*

(i) a person having ordinary skill in the art is deemed to be aware that (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride methanol solvate is an organic clathrate, that the guest molecules are mechanically imprisoned in the framework of the host and that the next higher homolog of methanol, i.e. ethanol, would be a close analog for such clathrate formation.

(ii) a person having ordinary skill in synthetic chemistry in possession of the exemplified process and product of methanol solvent by Kim '934 and the laboratory manual of Cheronis would be motivated to empirically modify the process with the next homologous alcohol with the expectation that the ethanol solvate with a different solubility can be obtained without pairing solvents."

Appellants respectfully traverse the rejection. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination [In re Geiger, 815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); In re Laskowski, 871 R.2d 115, 117, 10 U.S.P.Q.2d, 1397, 1399 (Fed. Cir. 1989))], and the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification [In re Gordon, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Circ. 1984)].

Furthermore, Appellants respectfully submit that Kim '934 never intended to prepare, isolate, characterize or describe a methanol solvate of the "title compound". Clearly, the purpose of Kim '934's unclaimed Example 2, columns 7 to 9, was to support enablement by demonstrating that Kim's chiral ketone intermediate (prepared by claimed processes) could be converted to and compared with the known sesquihydrate hydrochloride salt form of the "title compound" [(3S-cis)-2-(2-

chlorophenyl)-8-(3-hydroxy-1-methyl-4-piperidinyl)-5,7-dihydroxy-4H-1-benzopyran-4-one, also known as flavopiridol]. Kim '934 employed methanol in an overall process to prepare the said " title compound" that was isolated as 6.4 g of a pale yellow solid (column 9, lines 56-58) and characterized by comparison to the known sesquihydrate hydrochloride salt of flavopiridol. However, the ambiguous description of the penultimate 6.7 g solid as "title compound methanol" without supporting evidence to identify or confirm the form of the 6.7 g solid that was obtained coupled with the clear identification of Kim's '934 final 6.4 g solid "title compound" by NMR data and by comparison to melting point and optical rotation data that was reported for sesquihydrate hydrochloride salt of flavopiridol in US 4,900,727 (Kim '934 column, lines 56-67 vs Lit. 1 - see Appendix V, U.S. 4,900,727, column 18, table 9-continued, first line) fails to provide any motivation or suggestion that would cause one of ordinary skill in the art to pursue an alcohol solvate of the title compound, either alone or in combination with the Evans or Cheronis secondary references.

Appellants' application clearly states that the use of ethanol presents advantages over other solvents such as methanol (specification page 1, Appendix IV) and that the preferred form of applicants' ethanol solvate is the form that is essentially free from water (specification page 4, Appendix IV). The final form of the 6.4 g solid "title compound" obtained by Kim '934 (col. 9, lines 56-67) was compared with the known sesquihydrate hydrochloride salt of flavopiridol to confirm the identity of the title compound so obtained by Kim '934. That the final form of the title compound of Kim '934 is compared to the known sesquihydrate hydrochloride salt of the flavopiridol teaches away from obtaining an alcohol solvate hydrochloride salt form of flavopiridol. Furthermore, the comparison by Kim '934 of the final form of the "title compound" so isolated with the sesquihydrate hydrochloride salt of flavopiridol also teaches away from Appellants' ethanol solvate hydrochloride salt form of flavopiridol, particularly since the preferred form of Appellant's ethanol solvate hydrochloride salt of flavopiridol is essentially free from water. Appellant's submit that there is no teaching, suggestion or incentive from Kim '934, either alone or in combination with the cited Evans and Cheronis secondary references, that would motivate one of ordinary skill in the art to modify the process with the next homologous alcohol (ethanol) and with the expectation that the desired ethanol

solvate of the title compound would be obtained, preferably essentially free from water.

Discussion of the Advisory Action (Paper No. 15)

The Advisory Action indicated that the"proposed amendments would not be entered because allegedly new issues were raised that would require further consideration and /or search. Also, the Shutske declaration was considered but deemed not to place the application in condition for allowance for reasons stated in an attachment to the Advisory Action. The attachment to the Advisory Action consisted of three paragraphs numbered as paragraphs 1 to 3. The first two paragraphs of the Advisory Action read:

"The after final response with declaration of Shutske have been considered but are deemed to be not persuasive for the following reasons:

1. There is no good reason that why the declaration could not be submitted earlier since it was an opinion on terminology.

2. The opinion affidavit does not provide evidence as to "what" is the nature of the product disclosed by Kim '934. It has been clearly delineated in the office action that at col. 9 lines 19-57, the process for obtaining the product methanol was explicitly disclosed which indicated that the "product" was the "title compound (formula at lines 25-30) methanol". It does not matter whether the nomenclature of the product was according to standard practice or not, the product made by the process, is the one rendered the instant claims prima facie. Applicants provided no factual evidence that the "product" can not be a clathrate. It is noted that in patent law, it is the "product" that has patentability not its name. Please note that a patent can be obtained even if the name or nature of the product can not be ascertained i.e. a product by process."

In response to the first office action (Paper No. 7), Appellants specifically asserted that the phrase in Kim '934 "title compound methanol" [col. 9, lines 53-56] is ambiguous and not readily understood by one of ordinary skill in the art as to the meaning of the word methanol and that no data was provided to support the Office's assertion that a methanol solvate/clathrate of the title compound was indeed obtained by Kim '934. This issue was addressed earlier in this Appeal Brief. The

Office's continued assertion in the final office action (Paper No. 10) that the phrase "title compound methanol" is an explicit disclosure that indicated the 6.7 g product obtained by Kim '934 was indeed a clathrate or methanol solvate prompted submission of Shutske's declaration. Therefore, submission of Shutske's declaraton was justified and timely based on the Office's reiteration of its unsupported presumption that Kim '934 obtained a methanol solvate/clathrate form of the title compound in the Final Office Action.

In paragraph 2, the Office alleges that "*it does not matter whether the nomenclature of the product was according to standard practice or not, the product made by the process is the one rendered the instant claims prima facie.*" Appellants maintain that the phrase "title compound methanol" is not consistent with any acceptable nomenclature (whether or not it is according to standard practice), and that the phrase "title compound methanol" is ambiguous and fails to convincingly convey to one of ordinary skill in the art the true form of the 6.7 g title compound so obtained by Kim '934. The argument is not over nomenclature but rather the reasonable support for the Office's presumption as to the nature of Kim's '934 "title compound methanol".

Paragraph 2 of the Advisory Action then discusses that it is the product by process that should considered. A product by process discussion has not previously appeared in the prosecution history of this application. Moreover it begs the question that the overall process disclosed by Kim '934 has to be considered and not just a selected portion of the process. The overall process disclosed by Kim '934 includes taking the ambiguously described 6.7 g solid "title compound methanol" into water and lyophylizing to obtain 6.4 g of the "title compound" that was compared to the known sesquihydrate hydrochloride salt form of the title compound to confirm identity of the title compound finally isolated by Kim '934. Although the true form of the penultimate 6.7g "title compound methanol" obtained by Kim '934 cannot be ascertained or faithfully reproduced (as discussed earlier in this Appeal Brief), the overall process to afford the 6.4 g title compound is reproducible and the "title compound" so obtained was compared with the known sesquihydrate hydrochloride salt of the title compound. There is no evidence to support that Kim '934 obtained a methanol solvate form of the title compound either in the above-quoted sentence ending with "title compound methanol" nor in the overall process

that was described to afford the 6.4 g title compound, the identity of which is properly supported with comparative analytical data in Kim '934.

Appellants submit that Kim '934 does not teach the methanol solvate of the title compound. Appellants maintain that phrase "title compound methanol" is ambiguous and cannot be factually relied upon by one of ordinary skill in the art to support the assertion that a methanol solvate or clathrate was obtained by Kim '934. Appellants asserted *supra* that Kim '934 Example 2 (columns 7 to 9) clearly sought to prepare the known sesquihydrate hydrochloride salt of the title compound (flavopiridol) and specifically identified the 6.4 g title compound so obtained by NMR data and by comparison with melting point and optical rotation data that was reported for known sesquihydrate hydrochloride salt of flavopiridol in US 4,900,727. Appellants asserted in their July 25, 2002, reply to the first office action (Paper No. 7) on page 14, last paragraph, that the word "methanol" [in the phrase "title compound methanol] could be viewed as a simple drafting error and that the word "methanol" was not actually intended to be included in the above-quoted sentence from Kim '934 (col. 9, lines 53-56). Shutske's declaration subsequently substantiated that the phrase "title compound methanol" is ambiguous and also called attention to the omission of the word "hydrochlorde" from the phrase "title compound methanol" raising the issue that errors were associated with drafting at this point in the Kim '934 application. Clearly the phrase "title compound methanol" is ambiguous, possibly due to drafting mistake(s), and fails to provide factual support for the true form of the 6.7 g of title compound so obtained that was only described as "title compound methanol". As such, Appellant's assert that the Office inappropriately relied on its own interpretation of the ambiguous phrase "title compound methanol" without any factual or explanatory evidence (but rather with only impermissible hindsight reconstruction afforded by the instant application) as the basis for rejection of Appellant's claimed subject matter.

Paragraph 3 in the attachment to the Advisory Action reads:

"Further, factual evidence in the field which can be employed to support the postion that the character of Kim's '934 product by its process being clathrate can be found in issued patent US 6,576,647 which disclosed that it is conventionally known that cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-benzpyran-4-one will crystallized into solvates with

numerous solvents such as ethanol, DMSO, methanol.... (see col. 1 background). Further, at col. 8 the ethanol solvate of the compound was in possession by Bafus et al. '647 (copy will not be provided since it is assigned to the same assignee), thus a 102(f) issue, which is new, must be resolved."

As quoted above, paragraph 3 of the Advisory Action attachment alleges that factual evidence in the field, which can be employed to support the position that the character of Kim's '934 product by its process is a clathrate, can be found in issued US Patent 6,576,647 (Bafus et al. '647). Futhermore, the Office alleges that the ethanol solvate of the compound [flavopiridol] was in possession by Bafus et al. '647 and thus a 102(f) issue, which is new, must be resolved. However, no formal rejection based on 102(f) has been made to date.

In any event, Appellants submit the following facts concerning US 6,576,647 and the instant Kessler application:

1. US 6,576,647 and Kessler's instant application 09/760,590 were filed on the same day (January 16, 2001).

2. US 6,576,647 has claims directed to the anhydrous solvate-free hydrochloride salt form of flavopiridol and the instant Kessler application has claims directed to the ethanol solvate hydrochloride salt form of flavopiridol. Thus, the claimed inventions are different and distinct from each other.

3. US 6,576,647 and the instant Kessler application resulted from intracorporate work by several employees, each of whom had an obligation to assign their inventions at the time the invention was made to a subsidiary of Aventis SA. Therefore, the instant application and Bayfus '647 have a common assignee of record. In view of the foregoing, it is unclear what the Office is suggesting by the statement that US 6,576,647 provides factual evidence to support the proposition that the character of Kim's '934 product by its process is a clathrate. Since US 6,576,647 has the same filing date as Kessler's instant application, it is improper to suggest potential 102(f) issue, which is unambiguously erroneous.

In summary, Appellants maintain that solvates can display unique advantageous properties including different solubilities and characteristic X-ray diffraction patterns with respect to other forms of a compound. Appellants submit that well-defined solvate forms of a compound are not obvious just because a prior art

reference may employ a particular solvent as part of an overall process, absent supporting data or explanatory statements by the prior art to evidence that such a solvate was or could be formed (e.g. explicit art recognized naming of a solvate). Clearly, Kim'934 did not provide supporting data, explanatory statements or an explicit art-recognized name for the form of the compound that was ambiguously described as "title compound methanol" and that the Office conjectured was a methanol solvate . The Office appears to be taking a position that the mere teaching of a solvent as part of an overall process in the absence of supporting data or explanatory statements can be used to deprive a deserving inventor of the Constitutional right to obtain a patent for a novel, non-obvious and useful solvate form of a compound.

In view of the foregoing, the final rejection is untenable and should be overturned. Appellants respectfully request withdrawal of the final rejection and allowance of claims 10-19.

The Commissioner is hereby authorized to charge these fees and any other fees that are due to this paper to Deposit Account No. **18-1982** for Aventis Pharmaceuticals Inc., Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

Respectfully submitted,

Lawrence L. Martin

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APPENDIX

I Claims 10-19

II Shutske Declaration

III 298I from "Naming and Indexing of Chemical Substances for Chemical Abstracts"

IV Pages 1 and 4 from the Specification

V US 4,900,727

APPENDIX I

Claims 10-19

10. (new) Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate having an x-ray powder diffraction pattern,

D-Space (Å)
12.763
6.389
3.194
13.244
4.259

expressed in terms of D-spacing.

11. (new) Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate having an x-ray powder diffraction pattern,

D-Space (Å)	Relative Intensity
12.763	Strong
6.389	Medium
3.194	Weak
13.244	Weak
4.259	Weak
12.036	Weak
2.824	Weak
8.659	Weak
6.012	Weak
5.397	Weak
3.447	Weak

expressed in terms of D-spacing and relative intensity.

12. (new) Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate having an x-ray powder diffraction pattern,

2 Theta Angle (°)	D Space (Å)	Relative Intensity	Relative Intensity (%)
6.920	12.763	Strong	100.0
13.850	6.389	Medium	35.7
27.908	3.194	Weak	22.2
6.669	13.244	Weak	18.0
20.838	4.259	Weak	13.8
7.339	12.036	Weak	13.8
31.660	2.824	Weak	9.5
10.208	8.659	Weak	8.3
14.722	6.012	Weak	7.2
16.413	5.397	Weak	6.9
25.829	3.447	Weak	6.5

expressed in terms of 2 theta angle, D-spacing, relative intensity and % relative intensity.

13. (new) A process for the preparation of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate comprising:

a) dissolving a sufficient amount of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride in a sufficient amount of ethanol thus forming a mixture,

b) heating the mixture to about 50°C to about 80°C,

c) optionally filtering off undissolved material from the mixture, thus forming a solution,

d) concentrating the solution until about 50% to about 90% of the volatiles are removed,

e) cooling the solution and optionally isolating the obtained (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate crystals, and

f) optionally drying the obtained crystals.

14. (new) The process of claim 13 wherein the cooling of the solution is to about 0°C to about 10°C.

15. (new) Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate wherein said Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate is prepared by the process comprising:

a) dissolving a sufficient amount of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride in a sufficient amount of ethanol thus forming a mixture,

b) heating the mixture to about 50°C to about 80°C,

c) optionally filtering off undissolved material from the mixture, thus forming a solution,

d) concentrating the solution until about 50% to about 90% of the volatiles are removed,

e) cooling the solution and optionally isolating the obtained (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate crystals, and

f) optionally drying the obtained crystals.

16. (new) A pharmaceutical composition comprising a therapeutically effective amount of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate and a pharmaceutically acceptable carrier.

17. (new) A method of treating a patient for cancer by administering to said patient in need of such therapy a therapeutically effective amount of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate of claim 10.

18. (new) A method of treating a patient for cancer by administering to said patient in need of such therapy a therapeutically effective amount of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate of claim 11.

19. (new) A method of treating a patient for cancer by administering to said patient in need of such therapy a therapeutically effective amount of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate of claim 12.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Kurt M. Kesseler

Serial No.: **09/760,590**

Filed: **January 16, 2001**

Title: Ethanol Solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one

Examiner: Chang, C.

Art Unit: 1625

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Signature

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DECLARATION UNDER RULE 132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Gregory M. Shutske, declare that:

1. I received a B.S. in chemistry from Rose Polytechnic Institute, Terre Haute, Indiana, in 1971 and a Ph.D. in organic chemistry from the University of Indiana in 1975. I have been employed as a distinguished scientist at Aventis Pharmaceuticals Inc. and its predecessor companies, Hoechst Marion Roussel Inc. and Hoechst Roussel Pharmaceuticals Inc., since 1975. My research activities have been primarily in the field of organic chemistry and medicinal chemistry since about 1975. I am an author of about 55 peer-reviewed publications in the areas of organic chemistry and medicinal chemistry, and I am an inventor or co-inventor on about 65 U.S. patents.

2. I am an employee of Aventis Pharmaceuticals Inc. and I am not an inventor of the instant patent application. However, I have read the disclosures of the instant application and I am quite familiar with the disclosed and claimed subject matter therein.

3. I have also reviewed Kyoung Soon Kim U.S. patent 5,908,934 (Kim '934) and particularly column 9, Example 2-D, that describes the preparation of (3S-cis)-2-(2-chlorophenyl)-8-(3-hydroxy-1-methyl-4-piperidinyl)-5,7-dihydroxy-4H-1-benzopyran-4-one

that utilizes methodology and techniques well known to one of ordinary skill in the art of organic chemistry.

4. I have reviewed and understand the rejections of Claims 10-19 under 35 U.S.C. § 103(a) over Kim '934 in view of Cheronis and Evans, including the sentence of Example 2-D starting at column 9, line 53, of Kim '934 that reads "The precipitated solid was filtered, washed with ethyl ether three times and dried to afford a solid, 6.7 g which contained the title compound methanol." and is construed to be "consistent with the nomenclature of solvates/hydrates..." as is alleged by the examiner in the office action of November 6, 2002.

5. I believe certain portions of the Kim '934 Example 2-D to be ambiguous as written, most notably the phrase "title compound methanol" that appears in the sentence in column 9, starting at line 53, and reads "The precipitated solid was filtered, washed with ethyl ether three times and dried to afford a solid, 6.7 g which contained the title compound methanol." Although this affidavit is concerned with interpretation of the word "methanol" in the phrase "title compound methanol" of the quoted sentence, the phrase "title compound methanol" is the source of ambiguity for two reasons as will be discussed in paragraphs 6 and 7.

6. First, the quoted sentence discussed in paragraph 5 of this declaration implies that the "title compound" was obtained and the "title compound" of Example 2-D in Kim '934 is the name of the free base form of the compound. Careful reading of Example 2-D suggests that the "title compound hydrochloride" was obtained rather than the free base form of the compound. Supporting the fact that the "title compound hydrochloride" was obtained is an earlier description in Example 2-D of an acidification step with hydrochloric acid (Kim '934, column 9, lines 48-52). Further support that the "title compound hydrochloride" was obtained is provided by Kim '934's comparison of the melting point of the pale yellow solid obtained in column 9, line 58, to the literature reference 1 compound that is known to be the hydrochloride sesquihydrate form of the parent compound as is described in US 4,900,727 (reference 1). Thus the phrase "title compound" in the quoted sentence is ambiguous since it fails to properly describe the salt form of the compound that was obtained and this would suggest to one of ordinary skill in the art that an inadvertent omission of wording may have occurred within the phrase "title compound methanol".

7. The phrase "title compound methanol" discussed in paragraph 5 is also not written in explicit form that is consistent with art accepted or recognized language for the nomenclature of solvates or hydrates. Language to describe the solvate or hydrate form of a compound may be explicitly stated by several different art accepted or recognized phrases including "title compound methanolate", "title compound, methanol solvate", "title compound, compound with methanol", "title compound, compound with methanol (1:1)" [where the ratio of compound and solvent to each other is known and is illustrated by the designation (1:1)] and other such explicit phrases. Indeed the phrase "title compound methanol" may represent an incomplete description of the material obtained due to inadvertent omission of explicit wording not only with respect to the word "hydrochloride"as discussed in paragraph 6, but also with respect to art recognized description of a solvate as discussed in this paragraph. Thus, it is not possible for one skilled in the art to conclude with any certainty that a methanol solvate or clathrate was obtained from the phrase "title compound methanol" without additional supporting spectral data or physical evidence (e.g. elemental analysis), and Kim '934 does not provide such supporting data. Thus, one of ordinary skill in the art cannot confidently and unequivocally construe the sentence "The precipitated solid was filtered, washed with ethyl ether three times and dried to afford a solid, 6.7 g which contained the title compound methanol." to be "consistent with the nomenclature of solvates/hydrates." and the true form of the compound described as "title compound methanol" is not readily discernable from the description provided.

8. As a person signing below, I hereby declare that all statements made herein are of my own knowledge, are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 19th day of March 2003.

Gregory M. Shutske

APPENDIX IIII

Naming and Indexing of Chemical Substances for CHEMICAL ABSTRACTS

#16 Attach

A reprint of Appendix IV
(Chemical Substance Index Names)
from the CHEMICAL ABSTRACTS
1997 Index Guide

A publication of CHEMICAL ABSTRACTS SERVICE
Published by the American Chemical Society

Naming and Indexing of Chemical Substances for CHEMICAL ABSTRACTS

A publication of CHEMICAL ABSTRACTS SERVICE
Published by the American Chemical Society

A reprint of Appendix IV from *Chemical Abstracts* 1997 *Index Guide*

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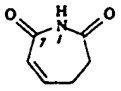
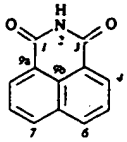
imide is expressed as a heterocyclic radical. The "diimide" of orthocarbonic acid, HN=C=NH ("carbodiimide") is indexed at **Methanediimine**, and its derivatives are often to be found at amine or amide headings.

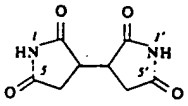
Examples:



1*H*-Azepine-2,7-dione, 3,4-dihydro- (not 2-Hexenimide)

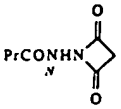


1*H*-Benz[*de*]isoquinoline-1,3-(2*H*)-dione (not 1,8-Naphthalenedicarboximide)

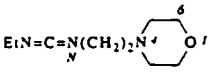


[3,3′-Bipyrrolidine]-2,2′,5,5′-tetrone (not 1,2,3,4-Butanetetracarboxylic 1,2:3,4-diimide

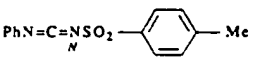
4*H*-1,3,2-Dithiazine, dihydro-1,1,3,3-tetraoxide (not 1,3-Propanedisulfonimide)



Butanamide, *N*-(2,4-dioxo-1-azetidinyl)-



4-Morpholineethanamine, *N*-(ethylcarbonimidoyl)-



Benzenesulfonamide, 4-methyl-*N*-(phenylcarbonimidoyl)-

For sulfur imides, see ¶ 200; for **Phosphine imide**, see ¶ 197.

192. Molecular addition compounds of neutral components are generally indexed in the *Chemical Substance* and *Formula Indexes* at the name and formula of each component. (The formula headings used are those of the components.) Some common components are not indexed unless all other components are also "common" or cannot be related to compound classes described in the "Order of Precedence of Compound Classes" (¶¶ 106); however, unesterified acids in the following list are indexed when not components of salts with bases. These common components are:

Acetic acid
Acetic acid, trifluoro-
Acetonitrile
Benzene
Benzene, methyl-
Benzene, 1,3,5-trinitro-
1,3-Benzenediol, 2,4,6-trinitro-
Benzenesulfonic acid
Benzenesulfonic acid, 4-methyl-
Benzoic acid
Borate(1−), tetrafluoro-, hydrogen
Butanedioic acid, 2,3-dihydroxy- (all stereoisomers)
2-Butenedioic acid (of defined or undefined stereochemistry)
Carbamimidothioic acid, phenylmethyl ester
Cyclohexanamine
Cyclohexanamine, *N*-cyclohexyl-
Ethanamine, *N*,*N*-diethyl-
Ethanedioic acid
Methane, dichloro-
Methanesulfonic acid
Phenol, 2,4,6-trinitro-
1,2,3-Propanetricarboxylic acid, 2-hydroxy-
3*H*-Pyrazol-3-one, 2,4-dihydro-5-methyl-4-nitro-2-(4-nitrophenyl)-
Pyridine

In addition, compounds with *water* and *ammonia* are not indexed at these names; they are expressed as "hydrate" and "ammoniate," with the prefixes mono, di, tri, etc. Fractional hydrates and ammoniates, such as hemi- and sesquihydrate, are named by use of a ratio as hydrate (2:1) and hydrate (2:3), respectively. Other solvates are indexed as molecular addition compounds. Often the solvate component receives the only entry, e.g., **Ethanol, compd. with pyridine (1:1)**. Crystal forms of organic compounds containing solvents of crystallization are indexed only as the unsolvated species except when properties of the crystals themselves are being studied. "Hydrates" of carbonyl compounds are indexed as *gem*-diols; e.g., "acetaldehyde hydrate" is indexed as 1,1-Ethanediol.

Ozonides of known structure are indexed by regular nomenclature; ozonides of unsaturated compounds are indexed at the compound headings with "ozonide" modification terms when the structures are unknown; "ozonides" of other compounds, e.g., phosphorus acid esters, are expressed as "compd. with ozone" and a ratio.

Bisulfite addition compounds are named as salts of specific hydroxy sulfonic acids when the structures are known or can reasonably be assumed, otherwise as a molecular addition compound of the carbonyl compound with a phrase such as "compd. with sodium hydrogen sulfite" and a ratio (if known) in the modification. An additional entry appears at **Sulfurous acid, compounds, monosodium salt, compd. with...** (This is an exception; an "oxo" acid salt ranks higher than an aldehyde or ketone (¶ 106) and would normally receive the preferred index entry.)

Diels-Alder adducts (diene adducts) of unknown constitution are indexed like molecular addition compounds, except that the "compd. with" phrase is replaced by "adduct with."

Catena compounds (cyclic compounds with interlocking rings) are indexed at the components with a "catena compd. with" phrase and a ratio.

Rotaxane is the term given to a stable anion of a linear molecule threaded through a cyclic molecule. The cyclic molecule is usually large, and the linear molecule usually has bulky end groups that prevent unthreading. These are indexed at the component names with a "rotaxane compd. with" phrase and a ratio.

The "preferred" index name (for molecular addition compounds that receive more than one) is that name to which cross-references in the *Index Guide* direct the reader from trivial names, the name given precedence in the CAS Registry System, and therefore the name which, after uninversion of the index heading if necessary, may be used among *CA* users in general discussions and reports. (To the index user in search of information, all the index names for an individual compound are of equal value.) For molecular addition compounds of stereoparents and their derivatives (¶ 203 I) with nonstereoparents, the preferred index entry appears at the former heading. In the absence of a stereoparent, the preferred index name is that which describes, in order of decreasing preference:

(*a*) a component other than a common component (see list above) selected according to the Order of Precedence of Compound Classes (¶ 106);

(*b*) a common component highest in the same order;

(*c*) a component which does not belong to any compound class described in the "Order of Precedence of Compound Classes," according to the earliest alphabetic position of the index name.

Examples ((*a*) is the preferred index name in each case):

1. (*a*) **2,5-Cyclohexadiene-1,4-dione, 2,3,5,6-tetrachloro-, compd. with coronene** (no ratio cited because unknown; functional compound preferred to cyclic hydrocarbon)

   (*b*) **Coronene, compd. with 2,3,5,6-tetrachloro-2,5-cyclohexadiene-1,4-dione**

2. (*a*) **Anthracene, compd. with 2,4,6-trinitrophenol (2:1)** (only entry; the cyclic hydrocarbon is preferred to a common compound of higher rank)

3. (*a*) **Methane, sulfinylbis-, compd. with iodine (1:1)** (by "iodine," the molecular form I_2 is implied; atomic forms are indicated, when necessary, by phrases such as "compd. with at. chlorine (1:2)" and an entry, in such a case, at **Chlorine, atomic**)

   (*b*) **Iodine, compd. with sulfinylbis[methane] (1:1)** (note that multiplied heading parents are bracketed in the uninverted names)

193. Nitrogen compounds. Cyclic nitrogen compounds, including lactams, sultams, and cyclic hydrazones, oximes, etc., are indexed at heterocyclic molecular skeletons (see *Section B*). Nitrogen-containing functional derivatives include imidic acids, amides, amines, imines, etc., for which the appropriate paragraph should be consulted. **Hydroxylamine** (see below) is a substitutive functional parent compound (¶ 130). Acyclic nitrogen skeletons, alone or with principal groups expressed as suffixes, are employed as heading parents for indexing purposes. Some groups, including azido, nitro, nitroso, and isocyano, are always expressed as substituent prefixes (¶ 132). *aci*-Nitro, HON(O)=, is also a mandatory prefix, and it may be substituted; e.g., (propyl-*aci*-nitro) is $CH_3CH_2CH_2ON(O)$=; (benzoyl-*aci*-nitro) is $C_6H_5C(O)ON(O)$=.

Diazene, HN=NH; **1-Triazene**, NH=N–NH$_2$; **Triazane**, NH$_2$–NH–NH$_2$, etc., are molecular skeleton heading parents to which the principal groups except hydroxy (and its chalcogen analogs), amino, and imino can be suffixed. **Hydrazine** is used as a trivial name for Diazane and its derivatives. Except for hydrazides (¶ 189) and hydrazones (¶ 190), alkyl, aryl and acyl derivatives are indexed at these nitrogen parents, which rank just below nitrogen heterocycles as the highest class of nonfunctional compounds (¶ 106). Within the class, seniority depends first on the number of hetero atoms, then on maximum unsaturation. When more preferred compound classes (including all those expressed

Ethanol Solvate of (-)-cis-2-(2-chloroph nyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one

BACKGROUND OF THE INVENTION

The compound (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or one of its pharmaceutically acceptable salt forms (known as "Flavopiridol") is an immunomodulator and antiinflammatory agent (U. S. Patent no. 4,900,727), and inhibitor of oncogene-encoded kinases or growth factor receptor tyrosine kinases (US Patent no. 5,284,856). Flavopiridol is a strong inhibitor of cyclin dependent kinases (CDKs) including CDK1, CDK2, CDK4, CDK6 and CDK7, (cdk1/clyclin B; cdk2/cyclin A; cdk2/cyclin E; cdk4/cyclinD; cdk6/cyclinD; cdk7/cyclin H) with the potential to cause inhibition of cell cycle progression in G_1 and G_2 by multiple mechanisms relatable to cdk inhibition. See *International Journal of Oncology* 9: 1143-1168 (1996). Also, Flavopiridol has been shown to inhibit the EGF receptor family, the receptor associated SRC family kinases, and signal transducing kinases. In vitro and in vivo experiments have shown that Flavopiridol is able to inhibit a broad type range of human tumors, leukemias and lymphomas.

(-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or a pharmaceutically acceptable salt thereof crystallizes into numerous solvates with solvents such as ethanol, DMSO, methanol, acetonitrile/isopropanol, ethanol/isopropanol, and isopropanol and solvate hydrates such as ethanol/ and isopropanol/water combinations. The superior solvate form is the Flavopiridol hydrochloride ethanol solvate form (hereafter "Form II").

The use of ethanol over the other solvents used to produce solvates presents advantages of less toxicity (e.g., methanol, isopropanol solvates).

A subject of the instant invention is Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one, this

Form II is hygroscopic. It can be used in water free form or in a form with a certain water content. The use in a form, which is essentially free from water is preferred.

Another subject of the instant invention is a process for the production of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one.Steps of the production process of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one are

a) dissolving a sufficient amount of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride in a sufficient amount of ethanol thus forming a mixture,

b) heating the mixture to about 50 to about 80 ° C;

c) optionally filtering off undissolved material from the mixture thus forming a solution

d) concentrating the solution until about 50 to about 90% of the volatiles are removed,

e) cooling the solution, for example, to about 0 to 10° C and optionally isolating (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride crystals thus obtained; and

f) optionally drying the crystals.

A "sufficient amount" of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride is that amount sufficient to be dissolved and heated according to the steps of the invention to form enough crystals to be recovered. Likewise, a "sufficient amount" of ethanol is that amount sufficient to dissolve at least a portion of the (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride added thereto in order to dissolve a portion thereof. These amounts can be experimentally determined.

The "volatiles" are those agents which may be evaporated during heating such as ethanol and/or water.

264811 1368 -00 02-13-90 45603

01-16-90 203746 78147.0 04900727 4451

United States Patent [19]

Kattige et al.

[11] Patent Number: 4,900,727

[45] Date of Patent: Feb. 13, 1990

[54] **4H-1-BENZOPYRAN-4-ONE COMPOUNDS WHICH HAVE ANTI-INFLAMATORY OR IMMUNODULATING ACTION**

[75] Inventors: **Samba L. Kattige; Ramchandra G. Naik; Aftab D. Lakdawalla; Aliihussein N. Dohadwalla; Richard H. Rupp; Noel J. de Souza,** all of Bombay, India

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[22] Filed: **Jan. 26, 1989**

Related U.S. Application Data

[63] Continuation of Ser. No. 36,478, Apr. 9, 1987, abandoned.

[30] **Foreign Application Priority Data**

Apr. 11, 1986 [DE] Fed. Rep. of Germany 3612337

[51] Int. Cl.[4] **A61K 31/445**; C07D 405/04

[52] U.S. Cl. **514/212**; 514/318; 514/320; 514/336; 514/422; 546/193; 546/196; 546/269; 540/596; 548/525

[58] Field of Search 546/193, 196, 269; 548/525; 540/596; 549/401; 514/212, 318, 320, 336, 422

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,603,137 7/1986 Bhat et al. 546/196

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Mar.; Advanced Organic Chemistry; pp. 439; 791.
Chemical Abstracts, vol. 91, No. 13, Abstract: 108119p, p. 597, 9/24/79.

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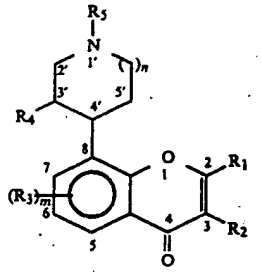
[57] **ABSTRACT**

The present invention relates to novel 4H-1-benzopyran-4-one derivatives, to processes for the preparation thereof and to their use as anti-inflammatory, analgesic, immuno-suppressive and anti-allergic agents. In particular, the present invention relates to novel compounds of the formula I,



in which R_1 is hydrogen, alkyl having 1 to 6 carbon atoms, arly-C_1–C_4-alkyl, substituted C_1–C_6-alkyl, C_3–C_6-cycloalkyl, C_3–C_6-cycloalkyl-C_1–C_4-alkyl, C_2–C_6-alkenyl, C_3–C_6-alkynyl, aryl or carboxyl or an aldehyde or COO—C_1–C_4-alkyl group, $R_2$is hydrogen, alkyl having 1 to 6 carbon atoms, nitro, amino, di-C_1–C_4-alkylamino or a halogen, R_3 is C_1–C_4-alkyl, substituted C_1–C_4-alkyl, hydroxyl, C_1–C_4-alkoxy, aryl-C_1–C_4-alkyl, nitro, amino, a C_1–C_4-alkylamino or di-C_1–C_4-alkylamino group or halogen, R_4 is hydrogen, hydroxyl, C_1–C_4-alkyoxy, C_1–C_4-alkyoxycarbonyl, aryloxy, amino or a C_1–C_4-alkylamino or di-C_1–C_4-alkylamino group, R_5 is hydrogen, C_1–C_6-alkyl, substituted C_1–C_6-alkyl, aryl-C_1–C_4-alkyl, C_3–C_6-cycloalkyl, C_3–C_6-cycloalkyl-C_1–C_4-alkyl, C_1–C_4-alkanoyl or aroyl, the aryl group being phenyl which is unsubstituted, monosubstituted or polysubstituted, m is an integer between 0 and 3 and n is an integer between 0 and 2, and to pharmacologically acceptable acid addition salts thereof.

12 Claims, 3 Drawing Sheets

FIG. 1

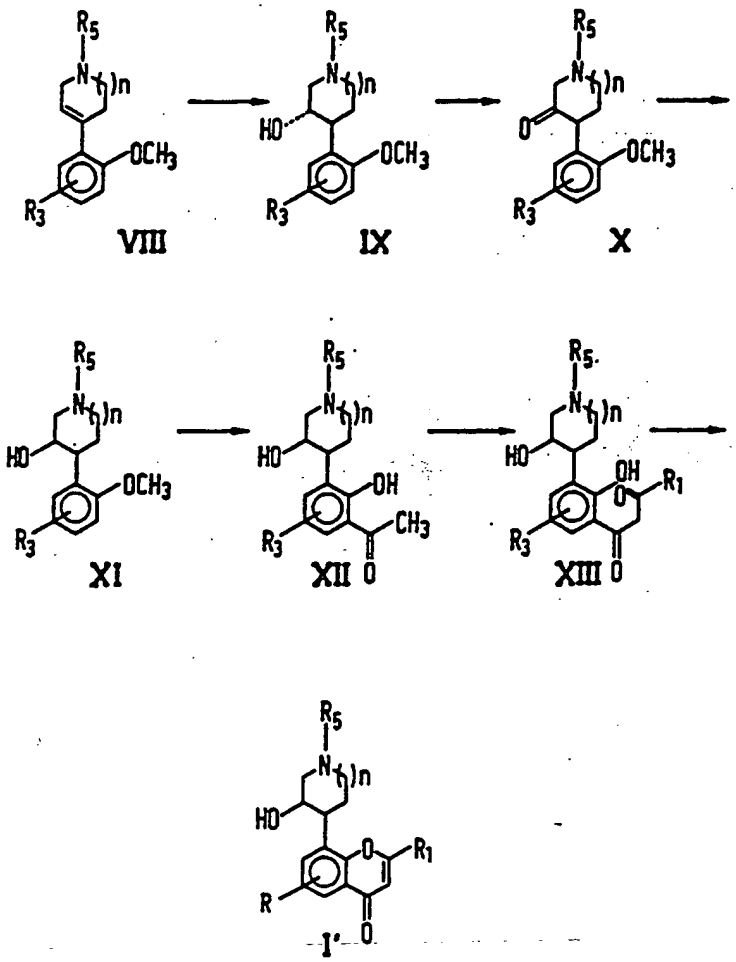


FIG. 2

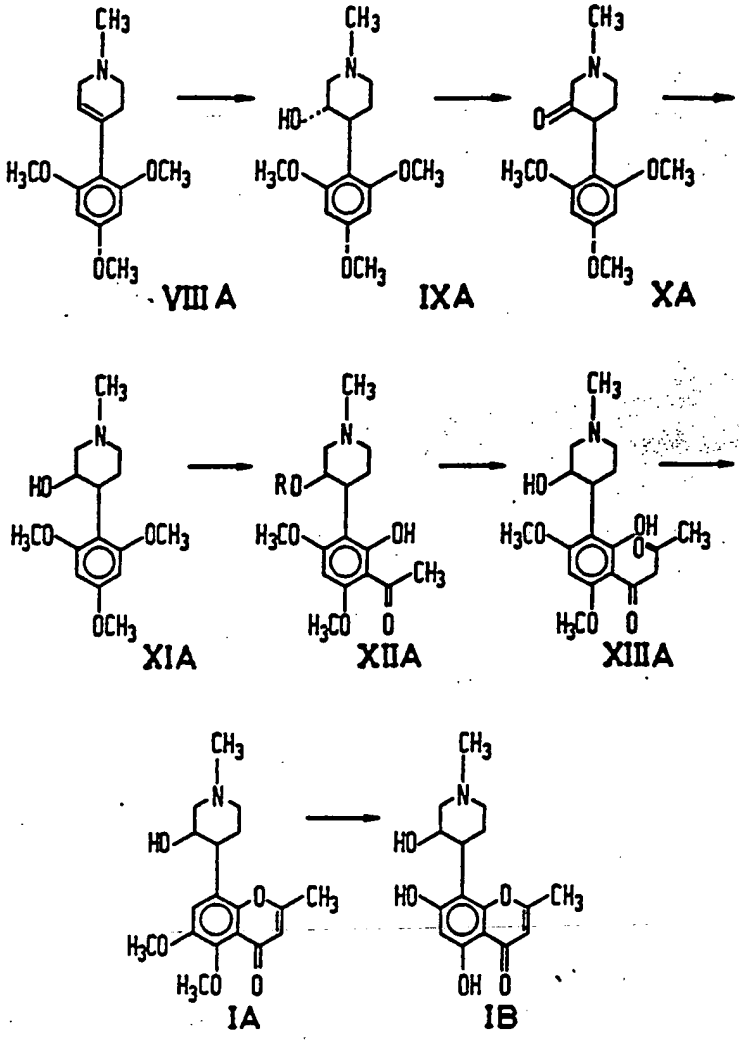
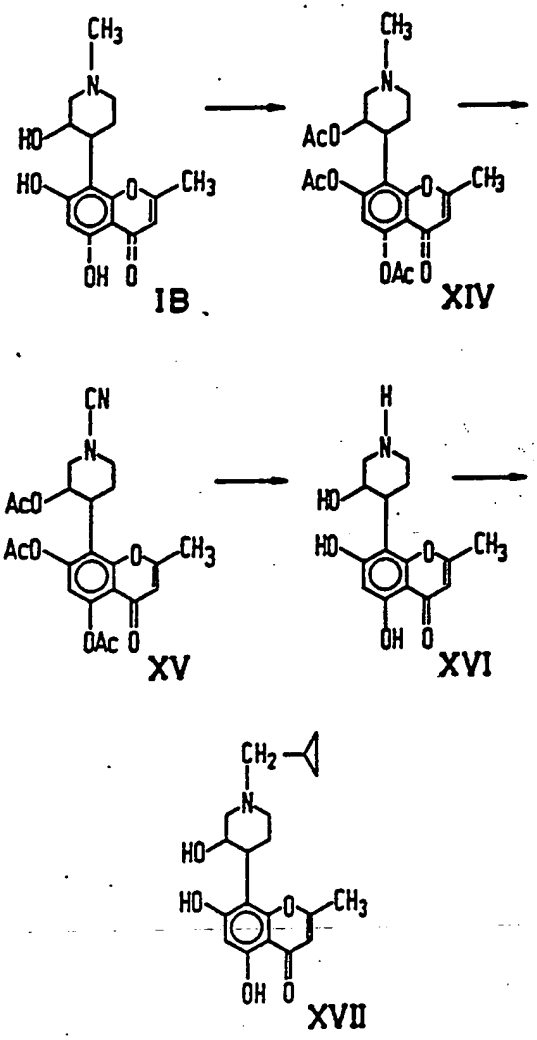


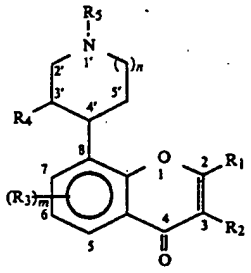
FIG.3


CH3
N
HO
HO
O
CH3
OH O
IB
AcO
AcO
OAc O
XIV
CN
AcO
AcO
OAc O
XV
H
HO
HO
OH O
XVI
CH2
HO
HO
CH3
OH O
XVII

4H-1-BENZOPYRAN-4-ONE COMPOUNDS WHICH HAVE ANTI-INFLAMATORY OR IMMUNODULATING ACTION

This application is a continuation of application Ser. No. 07/036,478 filed April 9, 1987, now abandoned.

The present invention relates to novel 4H-1-benzopyran-4-one derivatives, to processes for the preparation thereof and to their use as anti-inflammatory, analgesic, immunosuppressive and anti-allergic agents. In particular, the present invention relates to novel compounds of the formula I



in which

R_1 is hydrogen, alkyl having 1 to 6 carbon atoms, aryl-C_1–C_4-alkyl, substituted C_1–C_6-alkyl, C_3–C_6-cycloalkyl, C_3–C_6-cycloalkyl-C_1–C_4-alkyl, C_2–C_6-alkenyl, C_3–C_6-alkynyl, aryl, carboxyl or an aldehyde or COO-C_1–C_4-alkyl group,

R_2 is hydrogen, alkyl having 1 to 6 carbon atoms, nitro, amino, di-C_1–C_4-alkylamino or a halogen,

R_3 is C_1–C_4-alkyl, substituted C_1–C_4-alkyl, hydroxyl, C_1–C_4-alkoxy, aryl-C_1–C_4-alkyl, nitro, amino, a C_1–C_4-alkylamino or di-C_1–C_4-alkylamino group or halogen,

R_4 is hydrogen, hydroxyl, C_1–C_4-alkoxy, C_1–C_4-alkanoyloxy, C_1–C_4-alkoxycarbonyl, aryloxy, amino or a C_1–C_4-alkylamino or di-C_1–C_4-alkylamino group,

R_5 is hydrogen, C_1–C_6-alkyl, substituted C_1–C_6-alkyl, aryl-C_1–C_4-alkyl, C_3–C_6-cycloalkyl, C_3–C_6-cycloalkyl-C_1–C_4-alkyl, C_1–C_4-alkanoyl or aroyl, the aryl group being phenyl which is unsubstituted or mono or poly-substituted,

m is an integer between 0 and 3 and

n is an integer between 0 and 2,

and to pharmacologically acceptable acid addition salts thereof.

The compounds according to the invention have two asymmetric centers, one being at the linkage point of the nitrogen heterocyclic ring with the benzopyran moiety (C-4') and the other being at the carbon atom (C-3') substituted by R_4, so that two pairs of optical isomers are possible. It is to be understood that the definition of the compounds according to the invention includes all possible stereo isomers and their mixtures. In particular, both the racemic forms and the isolated optical isomers having the indicated activity are included. The two racemates can be resolved by physical methods such as fractional crystallization. The individual optical isomers are obtainable from the racemates by standard methods such as formation of the salt with an optically active acid and subsequent crystallization.

In EP-A2-0,137,193, the compound 5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one in the trans–(+)–form, its isolation from the plant Dysoxylum binectariferum and its use as an agent for immunomodulation have already been described. This racemate compound is therefore excepted from the present invention.

Examples of suitable alkyl groups R_1–R_5 are straight-chain or branched radicals having up to 6 and preferably up to 5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, t-butyl, pentyl or isopentyl groups.

Examples of suitable substituted alkyl groups R_1–R_5 are halogenoalkyl such as trifluoromethyl, hydroxyalkyl such as hydroxyethyl or carboxyalkyl such as carboxyethyl.

Suitable examples of a cycloalkyl group R_1 and R_5 having 3 to 6 carbon atoms are cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Cyclopropylmethyl is an example of cycloalkylalkyl.

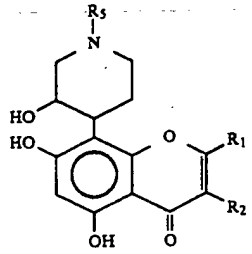
An example of an aralkyl group R_1 and R_5 is a phenylalkyl group in which the phenyl group is unsubstituted or mono- or poly-substituted by substituents such as halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro or a trifluoromethyl group.

An example of an aryl group R_1 and R_5 is a phenyl group which is unsubstituted or mono- or poly-substituted by substituents such as halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro or trifluoromethyl.

A suitable example of alkylamino R_1 and R_5 is $(CH_2)_n$-NR_6R_7, n being 1–3, and R_6 and R_7 being alkyl having the same meaning as that of alkyl R_1–R_5 above; moreover, R_6 and R_7, together with the nitrogen atom to which they are attached, can be a heterocyclic ring having one or more heteroatoms. Suitable examples of heterocyclic rings formed by R_6 and R_7, together with the nitrogen to which they are attached, are piperidine, pyrrolidine, morpholine, piperazine or imidazole, which can be unsubstituted or substituted in one or more positions by C_1–C_4-alkyl, C_1–C_4-alkoxy, aryl or a hydroxyl or amino group.

Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are the hydrochloride, hydrobromide, sulfate, phosphate, acetate, oxalate, tartrate, citrate, maleate or fumarate.

Preferred compounds are of the formula Ia



in which

R_1, R_2 and R_5 are as defined above and in particular:

R_1 is hydrogen or C_1–C_3-alkyl,

R_2 is hydrogen or C_1–C_3-alkyl and

R_5 is C_1–C_3-alkyl or C_3–C_5-cycloalkyl.

Particularly preferred compounds according to the invention are:

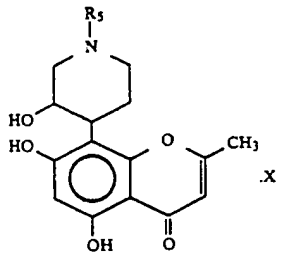
cis-(–)-5,7-dihydroxy-2-methyl-8-[4'-(1'-cyclopropylmethyl-3'-hydroxy)-piperidinyl]-4H-1-benzopyran-4-one,

cis-(+)-5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,

cis-(−)-5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-methyl-8-[4'-3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-ethyl-8-[4'-3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-n-propyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(+)-5,7-dihydroxy-2-n-propyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(−)-5,7-dihydroxy-2-n-propyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-2-n-butyl-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-phenyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(−)-5,7-dihydroxy-2-phenyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4'-3'-hydroxy-1'-methyl)-piperidinyl]-4H-benzopyran-4-one,
cis-(−)-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-2-(4-aminophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-2-(4-bromophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-2-(4-chlorophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-2-(2,4-dichlorophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-(4-fluorophenyl)-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxyl-2-(2-fluorophenyl)-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-(4-methylphenyl)-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-(2-pyridyl)-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,
cis-(±)-5,7-dihydroxy-2-(4-pyridyl)-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one.

Novel 4-H-1-benzopyran-4-one derivatives according to the invention are listed in Tables 1 to 5 below, reference being made to the following formulae:

Formula Ib



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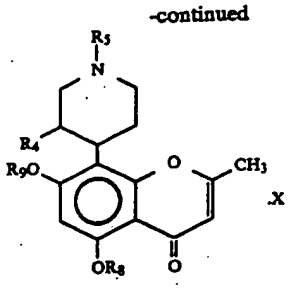
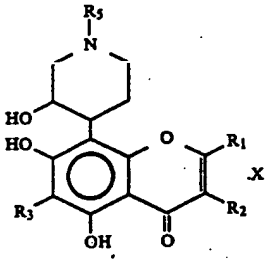
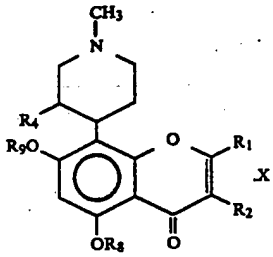
Formula Ic



Formula Id



Formula Ie



Formula If

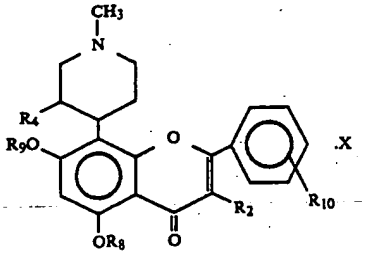


TABLE 1

	Compounds of formula Ib		
R_5	Melting point of the base	X	Melting point of the salt
H	>300°	—	—
CN	212–14°	—	—
CH_3	—	$HCl.\frac{1}{4}H_2O$	253–57°
C_2H_5	—	$HCl.H_2O$	>300°
CH_2CH_2CN	200–2°	—	—
p-Cl—C_6H_4—C(=O)—	—	H_2O	178–80°
$C_6H_4—CH_2—$	214–16°	—	—
$(CH_2)_2CH(CH_3)_2$	—	$HCl.3H_2O$	265–68°
CH_2COOK	—	$4.H_2O$	250–53° (Decomp.)
—C(=O)—CH_2COOCH_3	—	H_2O	185–88°

TABLE 1-continued

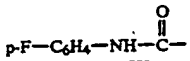
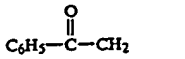
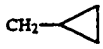
	Compounds of formula Ib		
R_5	Melting point of the base	X	Melting point of the salt
$CH_2-CH=CH_2$	—	HCl	235–38°
p-F—C_6H_4—CH_2	—	HCl	260–63°
	236–39°	—	—
p-F—C_6H_4—NH—C(=O)—			
p-CN—C_6H_4—CH_2	—	HCl.1½H_2O	224–26°
CH_2CH_2OH	—	CH_3OH	202–5°
m-CF_3—C_6H_4—CH_2	—	HCl.1½H_2O	173–75°
	—	HCl.½H_2O	>200°
C_6H_{11}	—	HCl.1½H_2O	>220°
$CH(CH_3)_2$	>210	—	—
	—	HCl.H_2O	>210

TABLE 1-continued

	Compounds of formula Ib		
R_5	Melting point of the base	X	Melting point of the salt
CH_3	—	cis(+)HCl	242–43°

TABLE 2

		Compounds of the formula Ic			
R_4	R_5	R_8	R_9	X	Melting point
OCOCH$_3$	CN	$COCH_3$	$COCH_3$	—	207–9°
$OCH_2CH=CH_2$	$CH_2CH=CH_2$	H	H	HCl	235–38°
OH(cis)	$CH_2CO_2C_2H_5$	H	$CH_2CO_2C_2H_5$	H_2O	185–88°
OH(trans)	CH_3	H	H	HCl.½H_2O	>290°
C—CH_2—C_6H_5	CH_3	H	H	—	238–40°
	CH_3	$COCH_3$	H	HCl.2H_2O	192–94°
	CH_3	H	H	HCl	195–99°
OH	CH_3	SO_2NH_2	H	H_2SO_4.2½H_2O	277–80°
OH(trans)	CH_3	CH_3	CH_3	—	>250
OH(cis)	CH_3	CH_3	CH_3	—	236–39°
OH(cis)	C_2H_5	CH_3	CH_3	HCl.½H_2O	240–42°
OH(cis)	CH_3	H	CH_3	HCl	230–32°

TABLE 3

		Compounds of the formula Id			
R_1	R_2	R_3	R_5	X	Melting point
CH_3	H	Br	CH_3	HCl	>300°
CH_3	$CH_2N(CH_3)_2$	Br	CH_3	2HCl.2H_2O	>300°
CH_3	NO_2	H	CH_3	HCl.1½H_2O	272–75° (Decomp.)
CH_3	Br	H	CH_3	—	275–76°
CH_3	NH_2	H	CH_3	HCl.H_2O	197–200°
H	H	H	CH_3	—	298° (Decomp.)
C_2H_5	H	H	CH_3	HCl.1½H_2O	230–33°
n-C_3H_7	H	H	CH_3	HCl.H_2O	190–92°

TABLE 4

					Compounds of the formula Ie		
R_1	R_2	R_4	R_8	R_9	X	Melting point	Optical rotation
H	H	OH	H	H	—	298° (Decomp.)	(±)
H	H	OH	CH_3	CH_3	HCl, 1.5H_2O	173–175	(±)
CH_3	H	OH	H	H	HCl,	237–240	(±)
CH_3	H	OH	H	H	HCl	243–43	(±)
CH_3	H	OH	H	H	HCl	241–42	(−)
CH_3	H	OH	H	CH_3	HCl	230–232	(±)
CH_3	H	OH	CH_3	CH_3	2HCl.2H_2O	236–239	(±)
CH_3	H	H	H	H	H_2O	232–233	(±)
C_2H_5	H	OH	H	H	HCl, 1.5H_2O	230–233	(±)
C_2H_5	H	OH	CH_3	CH_3	HCl. 1.5H_2O	240–242	(±)
n-C_3H_7	CH_3	OH	H	H	—	191–192	(±)
n-C_3H_7	H	OH	H	H	HCl	190–192	(±)
n-C_3H_7	H	OH	H	H	HCl, 0.5H_2O	197–200	(+)
n-C_3H_7	H	OH	H	H	HCl, 0.5H_2O	198–201	(−)
n-C_4H_9	H	OH	H	H	HCl, H_2O	157–159	(±)
CH_3	CH_3	OH	H	H	H_2O	232–233	(±)

TABLE 5

			Compounds of the Formula If		
R_{10}	R_8	R_9	X	Melting point	Optical rotation
H	H	H	HCl, 2H_2O	273–275°	(±)
4-NO_2	H	H	HCl, 3H_2O	249° (Decomp.)	(±)

TABLE 5-continued

Compounds of the Formula If					
R_{10}	R_8	R_9	X	Melting point	Optical rotation
4-NO_2	CH_3	CH_3	HCl, $2H_2O$	257–260° (Decomp.)	(±)
2-Cl	H	H	HCl, H_2O	198–200°	(±)
2-Cl	CH_3	CH_3	1.5HCl, H_2O	190–191°	(±)
4-NH_2	H	H	2HCl, $2H_2O$	240–242	(±)
3,5-Dimethoxy	CH_3	CH_3	2HCl, $2H_2O$	180–182°	(±)
4-Br	H	H	HCl, $2H_2O$	215°	(±)
4-Cl	H	H	HCl, $1.5H_2O$	225°	(±)
2,4-Dichloro	H	H	HCl, $2.5H_2O$	165–166	(±)
4-F	H	H	HCl, H_2O	285–287°	(±)
2-F	H	H	HCl, $2H_2O$	263–265	(±)
4-Methyl	H	H	HCl, $1.5H_2O$	247–49	(±)
3,5-Dihydroxy	H	H	HCl, $3H_2O$	300–302	(±)
3-Cl	H	H	HCl, $2H_2O$	288–290	(±)
3-Methyl	H	H	HCl, $2H_2O$	268°	(±)
2-Methyl	H	H		205–205	(±)
2-Cl	H	H	HCl, $2H_2O$	190–192	(+)
H	H	H	HCl,	269–271	(±)
3-Br	H	H	HCl, $2H_2O$	285°	(±)
3-CO_2Me	CH_3	CH_3	1.5HCl, $3H_2O$	235°	(±)
2,5-Dichloro	H	H	HCl, H_2O	251–252	(±)
3-COOH	CH_3	CH_3	HCl, $1.5H_2O$	270	(±)
2-Cl	H	H	HCl, $1.5H_2O$	190–194	(−)
H	H	H	HCl, $0.5H_2O$	266–69	(−)

The present invention also relates to a process for preparing compounds of the general formula I, which process comprises the steps sketched in the scheme in the attached FIG. 1. If desired, further chromone derivatives according to the invention can be obtained by treating compounds of the formula I' in FIG. 1 by known methods. The general scheme illustrated in FIG. 1 is explained and described in more detail by the reaction sequence illustrated in FIG. 2, which relates to the preparation of one of the preferred compounds according to the invention; it is here to be understood that the scope of the invention is not restricted thereby.

The preparation of the compound of the formula VIII with n=1 is known to those skilled in the art [S. M. McClavain and R. S. Berger, J. Am. Chem. Soc., 77, 2848 (1955); A. Ziering, L. Berger, S. D. Heineman and J. Lec., J. Org. Chem., 12, 894 (1947)]. Two methods are described in these papers. In the first method, 1,3,5-trimethoxybenzene is stirred with n-butyllithium at low temperatures, preferably between −60° and −90° C., in inert solvents such as hydrocarbons, for example pentane or hexane, or ether solvents, for example diethyl ether or tetrahydrofuran, to prepare the lithio salt which, on stirring with 1-methyl-4-piperidone and subsequent acidification, gives the tetrahydropyridine derivative. In the second and particularly preferred method, 1,3,5-trimethoxybenzene is stirred under acid conditions with 1-methyl-4-piperidone in solvents such as water, acetic acid, alcoholic solvents or a suitable mixture thereof, glacial acetic acid being particularly preferred.

Referring to the scheme in FIG. 2, the tetrahydropyridine derivative of the illustrated formula VIII (i.e. formula VIII with n=1) is hydroborinated, using diborane which forms directly by adding BF_3 etherate to a suspension of sodium borohydride in diethylene glycol dimethyl ether under anhydrous conditions and in an inert atmosphere maintained by continuously passing nitrogen or argon through. The reaction temperature is maintained between 20° and 90° C., but a temperature range of 50°–60° C. is preferred. The resulting organoborane complex is first treated with hydrochloric acid and then oxidized by addition of alkali and hydrogen peroxide. The compound thus obtained is a trans-alcohol of the formula IXA and this is converted by oxidation and subsequent reduction into the cis-alcohol of the formula XIA. The oxidation of the trans-alcohol of the formula IXA is carried out by means of a combination of reagents, namely acid chlorides, oxalyl chloride being preferred, dimethyl sulfoxide and triethylamine, and this is known to those skilled in the art as an oxidation by the method of Swern. The ketone of the formula XA, formed by oxidation of the compound of the formula IXA, is reduced by means of hyrdide reagents, preferably diborane, lithium borohydride or sodium borohydride. A fair number of solvents are compatible with sodium borohydride, but protic solvents such as methanol, ethanol and isopropanol are preferred. The cis-isomer can be obtained stereoselectively by maintaining a higher reaction temperature.

The cis-isomer can also be obtained by fractional crystallization of its acid addition salts which are formed with optically active acids such as, for example, (−)-and/or (+)-dibenzoyl tartaric acid.

If desired, the cis-isomer can also be esterified with an optically active acid such as (−)-menthyloxyacetic acid, and the resulting diestereomeric esters can then be separated by conventional methods such as fractional crystallization or chromatography.

The cis-hydroxy compound of the formula XIA is acetylated with acetic anhydride and acid catalysts such as aluminum chloride, boron trifluoride etherate and tin(IV) chloride, the particularly preferred reagent being boron trifluoride etherate. When using a large excess of boron trifluoride etherate, demethylation also takes place simultaneously, and only the desired methoxy group is demethylated regiospecifically, a compound of the formula XIIA being obtained, in which R is the radical —$COCH_3$. The hydrolysis of this compound with an alkali metal hydroxide leads to compounds of the formula XIIA with R=H. The compound of the formula XIIA is then converted into the chromone by methods known per se, of which two are described here. In the first method, the compound of the formula XIIA with R=H is stirred at room temperature in inert solvents, such as ether, tetrahydrofuran,

dioxane or hydrocarbon solvents such as hexane, with ethyl acetate and an alkali metal or NaH, preferably sodium metal; if the ester is a low-boiling liquid as in the present example, it can also be used as the solvent. The reaction is normally complete after one to ten hours and gives the diketone of the formula XIIIA with R=H, which is cyclized to give the chromone of the formula IA on stirring with mineral acids such as hydrochloric acid or sulfuric acid. In the second method, a compound of the formula XIIA is esterified with R=Ac, using a suitable acid, for example benzoic acid, and the resulting ester is stirred with a base such as, for example, an alkali metal hydroxide, in an inert solvent such as, for example, THF, dioxane or pyridine, the chromone of the formula IA being formed. The latter is demethoxylated with pyridine hydrochloride, in order to obtain the hydroxy compound of the illustrated formula IB. Using the corresponding esters in place of ethyl acetate, various 2-substituted chromones can be prepared.

In place of $AlCl_3$, BBr_3 or HBr/acetic acid, other acid reagents can also be used for demethoxylating the dimethoxychromone of the formula IA. The demethoxylation is effected by heating the dimethoxychromone derivatives with pyridine hydrochloride for a period of 2 to 10 hours to 180° C. In some cases, an addition of high-boiling amines to the pyridine hydrochloride can be advantageous.

The synthesis scheme according to FIG. 2 can be applied for the preparation of compounds of the formula I with R_5=H, alkyl (other than methyl), cycloalkyl, aralkyl and aryl. Compounds of the formula I, in which R_5 is as defined above, can also be prepared from the corresponding N-methyl compounds, i.e. $R_5=CH_3$ (compounds of the formula IB), by one of the known methods. A typical procedure can be seen from the scheme in FIG. 3, where a compound of the formula IB with $R_5=CH_3$, after protection of the hydroxyl groups, is treated with cyanogen bromide and then hydrolyzed under acidic or alkaline conditions to give compounds with R_5=H (compound of the formula XIV). On treatment with suitable electrophilic reagents, such as halides, acid chlorides, tosylates or enones, this compound gives compounds with R_5=alkyl, cycloalkyl, aralkyl or aryl, the compound of the illustrated formula XVII being a specific example. According to FIG. 3, 5,7-dihydroxy-2-methyl-8-[4'-(1'-cyclopropylmethyl-3'-hydroxy)-piperidinyl]-4H-1-benzopyran-4-one of the illustrated formula XVII is prepared by peracetylating 5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one of the formula IB with acetic anhydride and sodium acetate at 80°-90° C. The peracetylated product of the formula XIV is stirred with cyanogen bromide in chloroform and, in the presence of potassium carbonate, gives 5,7-diacetyl-2-methyl-8-[4'-(3'-acetoxy-1'-cyan)-piperidinyl]-4H-benzopyran-4-one of the formula XV, which, when heated for 5 hours with 2N hydrochloric acid to 110° C., gives the hydrolyzed and N-demethylated product 5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy)-piperidinyl]-4H-1-benzopyran-4-one of the formula XVI. On heating with cyclopropylmethyl chloride in isobutyl alcohol, this gives the N-cyclopropylmethyl derivative of the illustrated formula XVII.

Compounds of the formula I, in which R_2 is dialkylaminomethyl, are prepared by heating under reflux the corresponding chromone, where R_2=H, with a secondary amine hydrochloride and paraformaldehyde in dioxane or alcoholic solvents. Compounds of the formula I with $R_2=NO_2$ are appropriately prepared by stirring the corresponding chromone, where R_2=H, with acetic acid and concentrated nitric acid. Compounds of the formula I with $R_2=NH_2$ are obtained from the corresponding nitro derivatives by hydrogenation over 10% Pd/C.

Compounds of the formula I, in which one of the R_3 groups is bromine, are prepared by stirring the corresponding chromones, where R_3=H, with N-bromosuccinimide in dimethylformamide.

It is a further feature of the invention that the compounds according to the invention, represented by the formula I, possess pharmacological properties. In particular, they show an anti-inflammatory and immunomodulating action on laboratory animals. These properties are demonstrated by the results of the pharmacological tests which follow and which were carried out for evaluating the compounds according to the invention and their salts.

Systemic anti-inflammatory action on carrageenin-induced paw edema in rats

Male Charles Foster rats (120–150 g) were fasted for 18 hours, with water ad libitum. The test compound dissolved in distilled water was administered orally. The control group received distilled water. 0/05 ml of 0.5% carrageenin suspension was injected subcutaneously into the plantar region of the left hind paw. Using a Maclab differential volume meter, the paw volume was determined before the carrageenin injection and 3 and 6 hours after the injection. The percentage decrease in paw volume was calculated by the following equation:

$$\frac{\text{Vehicle control mean edema volume} - \text{Test group mean edema volume}}{\text{Vehicle control mean edema volume}} \times 100 = \text{\% decrease in paw volume}$$

The ED_{50} value was calculated from the dose/response curve. Six animals were used for each group.

The results with representative compounds according to the invention and their salts are listed in Table 4, the substituents relating to the following formula Ia:

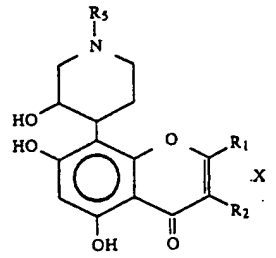
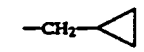


TABLE 6

Compounds of the formula Ia					
COMPOUND					
cis	R_1	R_2	R_5	X	ED_{50} mg/kg p.o.
(−)	CH_3	H		$HCl.H_2O$	10.0
(+)	CH_3	H	CH_3	HCl	9.4
(−)	CH_3	H	CH_3	HCl	9.0
(±)	CH_3	H	CH_3	HCl	12.5
(±)	C_2H_5	H	CH_3	$HCl.1.5\ H_2O$	10.5
(±)	n-C_3H_7	H	CH_3	$HCl.H_2O$	6.8
(−)	n-C_3H_7	H	H	HCl, $5\ H_2O$	5.8
(±)	Phenyl	H	H	HCl, $2\ H_2O$	5.7
(±)	2-chlorophenyl	H	H	HCl, H_2O	2.7
(±)	4-Aminophenyl	H	H	$2HCl, 2\ H_2O$	7.4
(±)	4-chlorophenyl	H	H	HCl, $1.5\ H_2O$	7.0
(±)	2,4-dichlorophenyl	H	H	HCl, $2.5\ H_2O$	5.7
(±)	4-fluorophenyl	H	H	HCl, H_2O	7.4
(±)	2-fluorophenyl	H	H	HCl, $2\ H_2O$	7.6
	2-Pyridyl	H	H	HCl, $5\ H_2O$	5.7
(−)	2-chlorophenyl	H	H	HCl, $2\ H_2O$	2.4
(−)	Phenyl	H	H	HCl, $5\ H_2O$	1.3

Reverse passive Arthus reaction (RPA) in rats

Charles Foster rats of both sexes, weighing 150–180 g, were sorted into groups of six animals each. 24 hours before the initiation of the RPA, the rats were shaved from the mid-dorsal region and fasted overnight. The test compounds were administered orally one hour before inducing the Arthus reaction. The RPA reaction was induced by intradermal injection of 0.1 ml of appropriately diluted rabbit anti-BSA serum. Immediately after the intradermal exposure, each rat received 0.5 ml of 0.4% bovine serum albumin intraveneously. Four hours after the intradermal challenge, each group of animals was killed by cervical dislocation. The full thickness of the skin was removed from the back of each animal, and a 12 mm diameter disk was punched out with a metal punch from the site of the antiserum injection. The wet weight of each skin site was determined as soon as possible. The edema caused by the RPA was measured as the difference (expressed in mg) between the wet weight of the site injected with antibody and that injected with normal rabbit serum.

The results are expressed as the percentage inhibition or potentiation of the edema by the compound as compared with the edema induced in the untreated control animals.

The results with representative compounds according to the invention and their salts are listed in Table 7.

TABLE 7

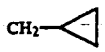
Action on the reverse passive Arthus reaction (RPA) on rats Compound of the formula Ia						
COMPOUNDS					DOSE mg/kg	%
cis	R_1	R_2	R_5	X	p.o.	inhibition
(−)	CH_3	H		$HCl.H_2O$	1.25	—
					2.5	23.0
					5.0	49.7
					10.0	—
					20.0	74.0
(+)	CH_3	H	CH_3	HCl	1.25	40.45
					2.5	48.78
					5.0	57.15
					10.0	50.37
					20.0	43.24
(−)	CH_3	H	CH_3	HCl	1.25	40.31
					2.5	39.11
					5.0	40.13
					10.0	45.17
					20.0	64.73
(±)	CH_3	H	CH_3	HCl	1.25	28.8
					2.50	31.8
					5.0	29.8
					10.0	35.8
					20.0	39.2
(±)	C_2H_5	H	CH_3	$HCl.1\frac{1}{4}H_2O$	1.25	16.0
					2.5	34.31
					5.0	41.65
					10.0	43.60
					20.0	77.10
(±)	n-C_3H_7	H	CH_3	$HCl.H_2O$	1.25	26.0
					2.50	32.0
					5.0	44.0
					10.0	55.0
					20.0	65.0

TABLE 7-continued

		Action on the reverse passive Arthus reaction (RPA) on rats Compound of the formula Ia				
		COMPOUNDS			DOSE mg/kg	%
cis	R_1	R_2	R_5	X	p.o.	inhibition
(−)	n-C_3H_7	H	CH_3	HCl.H_2O	1.25	—
					2.5	42.7
					5.0	41.3
					10.0	63.7
					20.0	72.1
(±)	Phenyl	H	CH_3	HCl.2H_2O	1.25	57.5
					2.5	55.6
					5.0	68.1
					10.0	90.6
					20.0	95.7
(±)	o-Chlorophenyl	H	CH_3	HCl.H_2O	1.0	37.0
					2.0	60.0
					4.0	80.0
(±)	2,4-Dichloro-phenyl	H	CH_3	HCl.2.5 H_2O	1.25	0
					2.5	41.7
					5.0	57.2
					10.0	49.5
					20.0	76.1
(±)	p-Fluorophenyl	H	CH_3	HCl.H_2O	1.25	24.4
					2.5	37.4
					5.0	61.5
					10.0	90.0
					20.0	86.2
(±)	o-Fluorophenyl	H	CH_3	HCl.2H_2O	1.25	0
					2.5	11.5
					5.0	52.7
(±)	2-Pyridyl	H	CH_3	HCl.1.5 H_2O	1.25	0
					2.5	12.0
					5.0	43.0
					10.0	90.0
					20.0	90.0
(−)	2-Chlorophenyl	H	CH_3	HCl.1,5 H_2O	1.25	34.0
					2.5	48.8
					5.0	70.0
					10.0	98.8
					20.0	—
(−)	Phenyl	H	CH_3	HCl.½H_2O	1.25	—
					2.5	26.2
					5.0	64.5
					10.0	92.2
					20.0	—

The invention is illustrated, but not restricted, by the examples which follow.

EXAMPLE 1

1-Methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine

N-methylpiperidone (2.8 mol) is added with stirring to a solution of trimethoxybenzene (2.38 mol) in glacial acetic acid (750 ml), the temperature of the reaction mixture being maintained below 25° C. After the addition has ended, hydrogen chloride is bubbled through the reaction mixture, which is heated for 3 hours to 95°–100° C. and then concentrated, and the residue is diluted with water. The aqueous solution is extracted with ether, the ether is separated off and the aqueous layer is rendered alkaline with concentrated sodium hydroxide solution. The precipitate thus obtained is filtered off, washed with water and dried. Recrystallization from petroleum ether (60°–80° C.) gives 500 g of 1-methyl-3-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine of melting point 118°–122° C.

Analysis: calculated for $C_{15}H_{21}NO_3.0.5H_2O$: C, 66.17; H, 8.08; N, 5.14%. Found: C, 67.75; H, 7.56; N, 5.03%.

EXAMPLE 2

(±)-trans-3-Hydroxy-4-(2,4,6-trimethoxyphenyl)-1-methylpiperidine

A solution of BF_3 etherate (42 ml) in diethylene glycol dimethyl ether (42 ml) is added dropwise to a cooled mixture of 1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (20 g) and sodium borohydride (12 g) in diethylene glycol dimethyl ether (140 ml). The mixture is heated for one hour to 50° C., and the cooled reaction mixture is then treated with water (20 ml) and then with concentrated HCl (116 ml). The mixture is stirred for two hours at 50°–60° C., cooled and rendered alkaline with sodium hydroxide solution. Hydrogen peroxide solution (30%, 20 ml) is then added and the mixture is heated with stirring for two hours at 50°–60° C. The solution is cooled and extracted with ethyl acetate. The ethyl acetate extract is concentrated in vacuo. The residue is acidified with 2N HCl and extracted with ethyl acetate, and the organic layer is separated off. The aqueous layer is then rendered alkaline with sodium hydroxide solution and extracted with ether. The ether extract is washed with brine, dried over sodium sulfate and concentrated, a solid residue being obtained which is recrystallized from hot water, which gives trans-3-

hydroxy-4-(2,4,6-trimethoxyphenyl)-1-methylpiperidine (12 g). Yield: 12 g; melting point 88°–89° C.

Analysis: compound as the oxalate, calculated for $C_{15}H_{23}NO_4.0.5(COOH)_2.1.75H_2O$: C, 56.5; H, 7.5; N, 4.12%. Found: C, 56.37; H, 8.14; N, 4.84%.

EXAMPLE 3

(+)-1-Methyl-4-(2,4,6-trimethoxyphenyl)-piperidin-3-one

Dimethyl sulfoxide (35 ml) is added dropwise under nitrogen to a solution, cooled to −60° C., of oxalyl chloride (20 ml) in dry methylene chloride (500 ml), and the mixture is stirred for 5–10 minutes. A solution of (±)-trans-3-hydroxy-4-(2,4,6-trimethoxyphenyl)-1-methylpiperidine (62 g) in methylene chloride (300 ml) is then added, while the temperature of the reaction mixture is held at −60° C. After the addition, the mixture is stirred for 15 minutes and triethylamine (155 ml) is added. The reaction mixture is then allowed to warm to a temperature of −30° C., diluted with water and rendered alkaline with sodium carbonate. The organic layer is separated off and the aqueous layer is extracted with ethyl acetate. The organic layers are combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give a solid residue which, on crystallization from isopropanol, gives the desired product (47 g) of melting point 110°–112° C.

Analysis: compound as the hydrochloride, calculated for $C_{15}H_{26}NO_4Cl$: C, 51.2; H, 7.39; N, 3.98; Cl, 10.09%. Found: C, 51.77; H, 7.16; N, 3.75; Cl, 11.45%.

EXAMPLE 4

(±)-cis-3-Hydroxy-4-(2,4,6-trimethoxyphenyl)-1-methylpiperidine

Sodium borohydride (10 g) is added with stirring to a solution, boiling under reflux, of 1-methyl-4-(2,4,6-trimethoxyphenyl)-piperidin-3-one in absolute ethanol. Stirring and heating under reflux is then continued for a further hour. On cooling, the reaction mixture is diluted with water, then concentrated in order to remove the ethanol and extracted with chloroform. The chloroform extract is washed with water, dried over anhydrous sodium sulfate and concentrated to give a solid residue which, on crystallization from acetone, gives the desired product (29.2 g) of melting point 124°–125° C.

Analysis: compound as the HCl salt; calculated for $C_{15}H_{24}NO_4Cl$: C, 56.69; H, 7.55; N, 4.4; Cl, 11.18%. Found: C, 56.78; H, 7.72; N, 3.93; Cl, 11.91%.

EXAMPLE 5

(±)-cis-3-Hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine

BF_3 etherate (107.6 ml) is added dropwise, with cooling in an icebath, to a solution of cis-3-hydroxy-4-(2,4,6-trimethoxyphenyl)-1-methylpiperidine (35 g) in methylene chloride (500 ml). 76.2 ml of acetic anhydride are then added dropwise. Subsequently, the reaction mixture is stirred for 24 hours at room temperature, diluted with water, rendered alkaline with sodium carbonate and extracted with methylene chloride. The extract is concentrated and the residue (37 g) is dissolved in methanol (200 ml) and stirred for 2 hours with 5% aqueous potassium hydroxide solution (500 ml). The mixture is then concentrated in vacuo and the residue is extracted with chloroform. The residue obtained after concentrating the chloroform extract is then purified by chromatography over silica gel, cis-3-hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine (28 g) of melting point 215°–218° C. (as the HCl salt) being obtained.

Analysis: compound as the HCl salt, calculated for $C_{16}H_{24}NO_5Cl$: C, 55.57; H, 6.94; N, 4.05; Cl, 10.27%. Found: C, 55.24; H, 7.04; N, 3.88; Cl, 10.40%.

EXAMPLE 6

General procedure for preparing cis/trans-5,7-dimethoxy-2-(R_1)-8-[4'-(3'-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-ones

The solution of cis/trans-3-hydroxy-4-(3'-acetyl-4,6-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine (1 equivalent) is stirred with a suitable ester (3 equivalents) and Na metal (~10 equivalents) or Na hydride (~5 equivalents) in dry dioxane or dimethylformamide at room temperature or at 70°–80° C. (see Table 8). Water is then added carefully and the mixture is extracted with chloroform. The organic phase is separated off, concentrated to some extent, saturated with HCl gas and then stirred for one hour. The solution is then rendered basic by addition of Na_2CO_3 and extracted with chloroform. The chloroform extract is dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by means of column chromatography (over silica gel). Thin-layer chromatography (5% methanol in $CHCl_3$ + 1% by volume of NH_4OH: Rf value 0.5–0.7) can then be carried out.

Using the general procedure indicated, the compounds listed in Table 8 which follows in Example 6a were prepared:

TABLE 8

Preparation of cis/trans compounds of the formula Ie (R_2 = H, R_4 = OH, R_5 and R_9 = CH_3; free base)

R_1	Ester	Solvent	Base	Temp.	Melting point °C.
Methyl (±)	Ethyl acetate	Ethyl acetate	Na	Reflux	236–38
Methyl (+)	Ethyl acetate	Ethyl acetate	Na	Reflux	228–29
Methyl (−)	Ethyl acetate	Ethyl acetate	Na	Reflux	228–30
Ethyl (±)	Ethyl propionate	Ethyl propionate	Na	70–80° C.	240–42 (HCl)
n-Propyl (±)	Ethyl butyrate	Dioxane	Na	70–80° C.	196–97
n-Propyl (+)	Ethyl butyrate	Dioxane	Na	70–80° C.	202–04
n-Propyl (−)	Ethyl butyrate	Dioxane	Na	70–80° C.	202–04
n-Butyl (±)	Ethyl valerate	Dioxane	Na	70–80° C.	
Phenyl (±)	Methyl benzoate	DMF	NaH	RT	232–34 (HCl)
Phenyl (−)	Methyl benzoate	DMF	NaH	RT	225–27
2-Chlorophenyl (±)	Methyl 2-chlorobenzoate	DMF	NaH	RT	190–91 (HCl)
2-Chlorophenyl (−)	Methyl 2-chlorobenzoate	DMF	NaH	RT	110
p-Bromophenyl (±)	Methyl 2-bromobenzoate	DMF	NaH	RT	167–70
p-Chlorophenyl (±)	Methyl 2-chlorobenzoate	DMF	NaH	RT	
2,4-Dichlorophenyl (±)	Methyl 2,4-dichlorobenzoate	DMF	NaH	RT	179–81 (HCl)

TABLE 8-continued

Preparation of cis/trans compounds of the formula Ie (R_2 = H, R_4 = OH, R_8 and R_9 = CH_3; free base)

R_1	Ester	Solvent	Base	Temp.	Melting point °C.
2-Fluorophenyl (±)	Methyl 2-fluorobenzoate	DMF	NaH	RT	
4-Fluorohenyl (±)	Methyl 4-fluorobenzoate	DMF	NaH	RT	212–14
4-Methylphenyl (±)	Methyl 4-methylbenzoate	DMF	NaH	RT	185
2-Pyridyl (±)	Methyl picolinate	DMF	NaH	RT	208–10
4-Pyridyl (±)	Methyl isonicotinate	DMF	NaH		215–17

EXAMPLE 6a

cis-5,7-Dimethoxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one

A solution of cis-3-hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine (10 g) in ethyl acetate (500 ml) is heated to reflux, and sodium (7 g) is added in small portions. The mixture is stirred and heated for 2 to 3 hours under reflux. After cooling, the mixture is diluted with water and the organic layer is separated off. The latter is then concentrated to half the volume, treated with concentrated HCl (10 ml) and stirred for about one hour. The mixture is then diluted with water, and the aqueous layer is rendered alkaline with Na_2CO_3 and extracted with chloroform. The chloroform extract is dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography over silica gel, the desired product (8 g) being obtained. Recrystallized from chloroform/petroleum ether, melting point 236°–238° C. (HCl salt).

Analysis: compound as the dihydrochloride, calculated for $C_{18}H_{25}NO_5Cl_2$: C, 50.46; H, 6.66; N, 2.68; Cl, 15.87%. Found: C, 49.80; H, 6.77; N, 3.27; Cl, 16.35%.

EXAMPLE 7

General demethylation procedure for the preparation of cis/trans-5,7-dihydroxy-2-(R_1)-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochlorides:

Dimethoxychromone (1.0 g), pyridine hydrochloride (5–10 g) and quinoline (0.5 ml) are mixed and heated for 2–3 hours to 180°–190° C. The reaction mixture is then allowed to cool, water (1 ml) is added and the mixture is rendered basic by addition of solid sodium bicarbonate. The semi-solid product is thoroughly extracted with 20% methanol in chloroform, and the organic phase is concentrated and purified by means of column chromatography (silica gel; 15% by volume of methanol in chloroform, with 1% by volume of added NH_4OH, as the eluent; Rf: 0.4–0.7). The hydrochloride salt is obtained by treatment with ethereal HCl.

Using the general procedure indicated, the compounds listed in Table 9 which follows and in Example 7a are prepared:

TABLE 9

(Formula Ie with R_2 = R_8 = R_9 = H, R_4 = OH)

R_1	X	Melting point °C.	$[\alpha]_D^{20}$
Methyl	HCl	237–240	(±)
Methyl	HCl	243	+29.5°
Methyl	HCl	241–242	−27.5°
Ethyl	HCl 1.5H_2O	230–233	(±)
n-Propyl	HCl, H_2O	190–192	(±)
n-Propyl	HCl, 0.5H_2O	197–200	+33.01°
n-Propyl	HCl, 0.5H_2O	198–201	−25.91
Phenyl	HCl, 2H_2O	273–275	(±)
Phenyl	HCl, H_2O	266–269	−50.4°
2-Chlorophenyl	HCl, H_2O	198–200	(±)

TABLE 9-continued

(Formula Ie with R_2 = R_8 = R_9 = H, R_4 = OH)

R_1	X	Melting point °C.	$[\alpha]_D^{20}$
2-Chlorophenyl	HCl, 1.5H_2O	190–194	−3.4°
4-Bromophenyl	HCl, 2H_2O	215	(±)
4-Chlorophenyl	HCl, 1.5H_2O	225	(±)
2,4-Dichlorophenyl	HCl, 2.5H_2O	165–166	(±)
2-Fluorophenyl	HCl, 2H_2O	263–265	(±)
4-Fluorophenyl	HCl, H_2O	285–287	(±)
4-Methylphenyl	HCl, 1.5H_2O	247–249	(±)
2-Pyridyl	HCl, 1.5H_2O	229	(±)
4-Pyridyl	2HCl, 2H_2O	278–280	(±)

EXAMPLE 7a

cis-5,7-Dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride

cis-5,7-Dimethoxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one (1.2 g), pyridine hydrochloride (8.0 g) and quinoline (0.5 ml) are mixed and heated for 2.5 hours to 180°–190° C. The mixture is cooled, water (1 ml) is added and the mixture is rendered alkaline by addition of solid sodium bicarbonate, and the semisolid product is thoroughly extracted with 20% methanol in chloroform. The organic layer is concentrated and purified by column chromatography over silica gel with 15% methanol in chloroform, containing 1% of NH_4OH, as the eluent. The product thus obtained is treated with ethereal HCl, giving the hydrochloride, yield 1.05 g, melting point 237°–240° C.

Analysis: compound as the HCl salt, calculated for $C_{16}H_{20}NO_5Cl$: C, 54.6; H, 6.07; N, 4.24; Cl, 10.77%. Found: C, 55.62; H, 6.49; N, 3.59; Cl, 9.84%.

EXAMPLE 8

Resolution of (±)-cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-piperidine

The racemic cis-3-hydroxy compound (90 g) is dissolved in methanol (300 ml), (−)-dibenzoyltartaric acid (126.4 g) in methanol (200 ml) is added, and the mixture is heated to the boil. Diisopropyl ether (about 500 ml) is then slowly added and the clear solution is allowed to cool, the tartrate salt crystallizing out slowly. The latter is filtered off and recrystallized five times from methanol/diisopropyl ether, $[\alpha]_D^{20}$ = +48.3° (MeOH). The tartrate salt (43 g) is suspended in water (200 ml), hydrochloric acid (2N, 100 ml) is added, and the mixture is stirred. The reaction mixture is extracted with five times 100 ml of ethyl acetate. The tartaric acid is recovered from the ethyl acetate extract. The aqueous layer is rendered alkaline with sodium carbonate and extracted with chloroform. The chloroform extract is dried over anhydrous sodium sulfate and concentrated,

the (+)-3-hydroxy compound, 17.7 g, melting point 109°–111° C., $[\alpha]_D^{20}=+53.81°$ (methanol), being obtained. The filtrates from the tartrate crystallizations are combined, and the free base is recovered as described above. The free base (20 g) is dissolved in methanol (110 ml), (+)-dibenzoyltartaric acid (29 g) is added, and the solution is heated to the boil. Diisopropyl ether (110 ml) is then added slowly. On standing at room temperature, the tartrate crystallizes out. It is filtered off and recrystallized three times from a methanol/diisopropyl ether mixture. Yield: 20.2 g, $[\alpha]_D^{20}=-49°$ (MeOH). The free base is isolated as described above, yield: 8.2 g, melting point 109°–111° C., $[\alpha]_D^{20}=-54.13°$ (methanol).

Optically pure isomers were prepared from optically pure (+)- or (−)-cis-3-hydroxy-4-(3-acetyl-4,6-dimethoxy-2-hydroxy)-phenyl-1-methylpiperidine as in Examples 9 and 10 which follow:

EXAMPLE 9

(−)-cis-3-Hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine

(−)-cis-3-Hydroxy-4-(2',4',6'-trimethoxyphenyl)-1-methyl-piperidine is treated in the same way as in Example 5, giving (−)-cis-3-hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine of melting point 184°–86° C., $[\alpha]_D^{20}=-32.63°$ (MeOH, c=0.614).

EXAMPLE 10

(+)-cis-3-Hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine

(+)-cis-3-Hydroxy-4-(2',4',6'-trimethoxyphenyl)-1-methylpiperidine is treated in the same way as in Example 5, giving (+)-cis-3-hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine of melting point 184°–85° C., $[\alpha]_D^{20}=+34.47°$ (MeOH, c=0.586).

EXAMPLE 11

(−)-cis-5,7-Dimethoxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one

(−)-cis-3-Hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine is treated in the same way as in Example 6, giving (−)-cis-5,7-dimethoxy-2-methyl-8-[4'-3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one of melting point 228°–30° C., $[\alpha]_D^{20}=-80.59°$ (MeOH, c=0.59).

EXAMPLE 12

(+)-cis-5,7-Dimethoxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one

(+)-cis-3-Hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine is treated in the same way as in Example 6, giving (+)-cis-5,6-dimethoxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one of melting point 228°–29° C., $[\alpha]_D^{20}=+84.1°$ (MeOH, c=0.618).

EXAMPLE 13

(−)-cis-5,7-Dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride

(−)-cis-5,7-Dimethoxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one is treated in the same way as in Example 7, giving (−)-cis-5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride f melting point 242°–45° C., $[\alpha]_D^{20}=-25.37°$ (MeOH, c=0.653).

EXAMPLE 14

(+)-cis-5,7-Dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride

(+)-cis-5,7-Dimethoxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one is treated in the same way as in Example 7, giving (+)-cis-5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride of melting point 242°–44° C., $[\alpha]_D^{20}=+29.57°$ (MeOH, c=0.58).

EXAMPLE 15

cis-5,7-Dihydroxy-2-ethyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride

cis-3-Hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine is treated in Example 6 with ethyl propionate in place of ethyl acetate, and the product is demethoxylated as described in Example 7, giving cis-5,7-dihydroxy-2-ethyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride of melting point 230°–33°.

Analysis: calculated for $C_{19}H_{25}NO_5.HCl0.5H_2O$: C, 53.3; H, 6.53; N, 3.66; Cl, 9.28%. Found: C, 53.1; H, 6.51; N, 3.83; Cl, 9.45%.

EXAMPLE 16

cis-5,7-Dihydroxy-2-n-propyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride

cis-3-Hydroxy-4-(3'-acetyl-4',6'-dimethoxy-2'-hydroxy)-phenyl-1-methylpiperidine is treated as in Example 6 with ethyl butyrate in place of ethyl acetate, and the product is demethoxylated as described in Example 7, giving cis-5,7-dihydroxy-2-n-propyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride of melting point 190°–92° C.

Analysis: calculated for $C_{20}H_{27}NO_5.HCl.H_2O$: C, 55.74; H, 6.70; N, 3.61; Cl, 9.16%. Found: C, 56.25; H, 6.65; N, 3.52; Cl, 9.39%.

EXAMPLE 17

cis-(−)-5,7-Dihydroxy-2-methyl-8-[4'-(3'-hydroxy)-piperidinyl]-4H-benzopyran-4-one

cis-(−)-5,7-Dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one (5 g) is heated for 12 hours to 90° C. with acetic anhydride (25 ml) and sodium acetate (4.5 g). The acetic anhydride is distilled off in a high vacuum and the residue is stirred up with ethyl acetate. The fraction soluble in ethyl acetate is concentrated to dryness. The residue is dissolved in dry chloroform (27 ml), anhydrous potassium carbonate (5 g) is added and the mixture is cooled to 0° C. Cyanogen bromide (6 g) in dry chloroform (25 ml) is added dropwise. After the addition, the reaction mixture is stirred for 4–5 hours at 40°–50° C. and filtered, and the filtrate is washed with a small quantity of brine, dried over anhydrous sodium sulfate and concentrated. The residue is heated for 7–8 hours with 1N hydrochloric acid (30 ml) on a steam bath. The reaction mixture is rendered alkaline by addition of solid sodium carbonate and concentrated. The residue is allowed to run

through an HP-20 column, and the product is eluted with 20% MeOH in H_2O. The product is crystallized from MeOH/diisopropyl ether, melting point 300° C., $[\alpha]_D^{20} = -11.38°$ (MeOH, c=0.9).

Analysis: compound as the hydrochloride salt, calculated for $C_{15}H_{18}NO_5Cl$: C, 55.00; H, 5.53; N, 4.27; Cl, 10.81%. Found: C, 54.33; H, 5.59; N, 3.93; Cl, 11.21%.

EXAMPLE 18

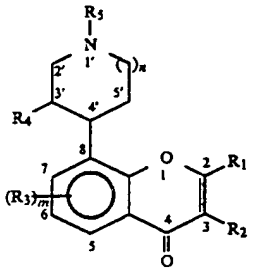
cis-(−)-5,7-Dihydroxy-2-methyl-8-[4'-(1'-cyclopropylmethyl-3'-hydroxy)-piperidinyl]-4H-1-benzopyran-4-one hydrochloride

cis-(−)-5,7-Dihydroxy-2-methyl-8-[4'-(3'-hydroxy)-piperidinyl]-4H-1-benzopyran-4-one (1.0 g), cyclopropyl methyl ketone (1.5 ml), isobutanol (15 ml) and potassium carbonate (3 g) are mixed and heated for 15 hours to 90° C. The reaction mixture is filtered and the residue is washed with chloroform. The filtrate is concentrated and purified by column chromatography over silica gel. The compound is eluted with 6% MeOH in chloroform. The hydrochloride is prepared by addition of ethereal HCl, yield 0.7 g, melting point 249°–51° C., $[\alpha]_D^{20} = -35.4°$ (MeOH, c=0.571).

Analysis: calculated for $C_{19}H_{26}NO_6Cl$: C, 57.07; H, 6.51; N, 3.75; Cl, 8.87%. Found: C, 57.18; H, 6.51; N, 3.75; Cl, 9.44%.

We claim:

1. A compound of the formula I



I

in which:

R_1 is hydrogen, unsubstituted C_1–C_6-alkyl, C_1–C_6 alkyl substituted by halogen, hydroxy or carboxy, phenyl-C_1–C_4-alkyl wherein the phenyl is unsubstituted or mono- or polysubstituted by halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro or trifluoromethyl, C_3–C_6-cycloalkyl, C_3–C_6-cycloalkyl-C_1–C_4-alkyl, C_2–C_6-alkenyl, C_3–C_6-alkynyl, phenyl which is unsubstituted or mono- or polysubstituted by halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro, trifluoromethyl, amino or hydroxy, or is carboxyl, an aldehyde or -COO-C_1–C_4-alkyl group, or 2- or 4-pyridyl,

R_2 is hydrogen, C_1–C_6-alkyl, nitro, amino, di-C_1–C_4-alkylamino or di-C_1–C_4-alkylaminomethyl or a halogen atom,

R_3 is unsubstituted C_1–C_4-alkyl, C_1–C_4-alkyl substituted by halogen, hydroxy or carboxy, hydroxyl, C_1–C_4-alkoxy, phenyl-C_1–C_4-alkyl wherein the phenyl is unsubstituted or mono- or polysubstituted by halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro or trifluoromethyl, nitro, halogen, amino, C_1–C_4-alkylamino or di-C_1–C_4-alkylamino,

R_4 is hydrogen, hydroxyl, C_1–C_4-alkoxy, C_1–C_4-alkanoyloxy, C_1–C_4-alkoxycarbonyl, phenoxy which is unsubstituted or mono- or polysubstituted by halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro or trifluoromethyl, amino, C_1–C_4-alkylamino or di-(C_1–C_4-alkyl)-amino,

R_5 is hydrogen, unsubstituted C_1–C_6-alkyl, C_1–C_6-alkyl substituted by halogen, hydroxy or carboxy, phenyl-C_1–C_4-alkyl wherein the phenyl is unsubstituted or mono- or polysubstituted by halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro or trifluoromethyl, C_3–C_6-cycloalkyl, C_3–C_6-cycloalkyl-C_1–C_4-alkyl, C_1–C_4-alkanoyl or phenylcarbonyl which is unsubstituted or mono- or polysubstituted by halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, nitro or trifluoromethyl,

n is an integer between 0 and 2 and

m is an integer between 0 and 3,

with the exception of the compound 5,7-dihydroxy-2-methyl-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one,

or a pharmacologically acceptable acid addition salt or optical isomer thereof.

2. A compound as claimed in claim 1, wherein R_1, R_2 and R_5 are as defined, R_3 and R_4 are a hydroxyl group, m is the number 2 and n is the number 1.

3. A compound as claimed in claim 1, wherein R_1 is hydrogen or C_1–C_3-alkyl, R_2 is hydrogen or C_1–C_3-alkyl, R_3 and R_4 are each a hydroxyl group, R_5 is C_1–C_3-alkyl or C_3–C_5-cycloalkyl, m is the number 2 and n is the number 1.

4. cis-(±)-2-(2-Chlorophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one or a pharmacologically acceptable acid addition salt thereof.

5. cis-(−)-2-(2-Chlorophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one or a pharmacologically acceptable acid addition salt thereof.

6. cis-(−)-2-Phenyl-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one or a pharmacologically acceptable acid addition salt thereof.

7. cis-(±)-2-Phenyl-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one or a pharmacologically acceptable acid addition salt thereof.

8. cis-(±)-2-(p-Fluorophenyl)-5,7-dihydroxy-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-1-benzopyran-4-one or a pharmacologically acceptable acid addition salt thereof.

9. cis-(±)-2-(2-Pyridyl)-8-[4'-(3'-hydroxy-1'-methyl)-piperidinyl]-4H-benzopyran-4-one or a pharmacologically acceptable acid addition salt thereof.

10. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of the formula I as claimed in claim 1, or a pharmacologically acceptable acid addition salt thereof, and a pharmaceutically acceptable carrier.

11. A method for the treatment of a human or animal in need of anti-inflammatory or immunomodulating action which comprises administering to said human or animal an amount effective for said treatment of the pharmaceutical composition as claimed in claim 10.

12. A method for the treatment of a human or animal in need of anti-inflammatory or immunomodulating action which comprises administering to said human or animal an amount effective for said treatment of a compound of the formula I as claimed in claim 1.

* * * * *